

*sub A1*  
**(R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols**  
**Useful for Inhibiting Cholesteryl Ester Transfer Protein Activity**

*INS*  
*12*

## FIELD OF THE INVENTION

5

This invention is in the field of treating cardiovascular disease, and specifically relates to compounds, compositions, methods for treating atherosclerosis and other coronary artery disease, and methods for making compounds of this invention. More particularly, the invention relates to (R)-  
 10 chiral halogenated 1-substitutedamino-(n+1)-alkanol compounds that inhibit cholesteryl ester transfer protein (CETP), also known as plasma lipid transfer protein-I.

## BACKGROUND OF THE INVENTION

15

Numerous studies have demonstrated that a low plasma concentration of high density lipoprotein (HDL) cholesterol is a powerful risk factor for the development of atherosclerosis (Barter and Rye, *Atherosclerosis*, 121, 1-12 (1996)). HDL is one of the major classes of lipoproteins that function in the  
 20 transport of lipids through the blood. The major lipids found associated with HDL include cholesterol, cholesteryl ester, triglycerides, phospholipids and fatty acids. The other classes of lipoproteins found in the blood are low density lipoprotein (LDL) and very low density lipoprotein (VLDL). Since low levels of HDL cholesterol increase the risk of atherosclerosis, methods for  
 25 elevating plasma HDL cholesterol would be therapeutically beneficial for the treatment of atherosclerosis and other diseases associated with accumulation of lipid in the blood vessels. These diseases include, but are not limited to, coronary heart disease, peripheral vascular disease, and stroke.

Atherosclerosis underlies most coronary artery disease (CAD), a major  
 30 cause of morbidity and mortality in modern society. High LDL cholesterol (above 180 mg/dl) and low HDL cholesterol (below 35 mg/dl) have been shown to be important contributors to the development of atherosclerosis. Other diseases, such as peripheral vascular disease, stroke, and hypercholesterolaemia are negatively affected by adverse HDL/LDL ratios.  
 35 Inhibition of CETP by the subject compounds is shown to effectively modify plasma HDL/LDL ratios, and to check the progress and/or formation of these diseases.

CETP is a plasma protein that facilitates the movement of cholesteryl esters and triglycerides between the various lipoproteins in the blood (Tall, *J. Lipid Res.*, 34, 1255-74 (1993)). The movement of cholesteryl ester from HDL to LDL by CETP has the effect of lowering HDL cholesterol. It therefore follows that inhibition of CETP should lead to elevation of plasma HDL cholesterol and lowering of plasma LDL cholesterol, thereby providing a therapeutically beneficial plasma lipid profile (McCarthy, *Medicinal Res. Revs.*, 13, 139-59 (1993); Sitori, *Pharmac. Ther.*, 67, 443-47 (1995)). This exact phenomenon was first demonstrated by Swenson et al., (*J. Biol. Chem.*, 264, 14318 (1989)) with the use of a monoclonal antibody that specifically inhibited CETP. In rabbits, the antibody caused an elevation of the plasma HDL cholesterol and a decrease in LDL cholesterol. Son et al. (*Biochim. Biophys. Acta* 795, 743-480 (1984)), Morton et al. (*J. Lipid Res.* 35, 836-847 (1994)) and Tollefson et al. (*Am. J. Physiol.*, 255, (Endocrinol. Metab. 18, E894-E902 (1988))) describe proteins from human plasma that inhibit CETP. U.S. Patent 5,519,001, issued to Kushwaha et al., describes a 36 amino acid peptide derived from baboon apo C-1 that inhibits CETP activity. Cho et al. (*Biochim. Biophys. Acta* 1391, 133-144 (1998)) describe a peptide from hog plasma that inhibits human CETP. Bonin et al. (*J. Peptide Res.*, 51, 216-225 (1998)) disclose a decapeptide inhibitor of CETP. A depsipeptide fungal metabolite is disclosed as a CETP inhibitor by Hedge et al. in *Bioorg. Med. Chem. Lett.*, 8, 1277-80 (1998).

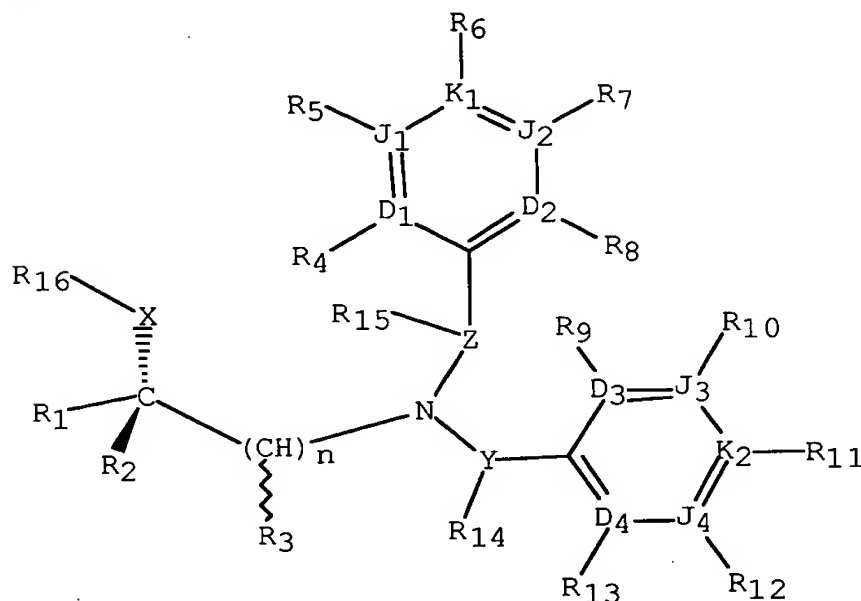
There have been several reports of non-peptidic compounds that act as CETP inhibitors. Barrett et al. (*J. Am. Chem. Soc.*, 118, 7863-63 (1996)) and Kuo et al. (*J. Am. Chem. Soc.*, 117, 10629-34 (1995)) describe cyclopropane-containing CETP inhibitors. Pietzonka et al. (*Bioorg. Med. Chem. Lett.*, 6, 1951-54 (1996)) describe phosphonate-containing analogs of cholesteryl ester as CETP inhibitors. Coval et al. (*Bioorg. Med. Chem. Lett.*, 5, 605-610 (1995)) describe Wiedendiol-A and -B, and related sesquiterpene compounds as CETP inhibitors. Japanese Patent Application No. 10287662-A describes polycyclic, non-amine containing, polyhydroxylic natural compounds possessing CETP inhibition properties. Lee et al. (*J. Antibiotics*, 49, 693-96 (1996)) describe CETP inhibitors derived from an insect fungus. Busch et al. (*Lipids*, 25, 216-220, (1990)) describe cholesteryl acetyl bromide as a CETP inhibitor. Morton and Zilversmit (*J. Lipid Res.*, 35, 836-47 (1982)) describe that p-chloromercuriphenyl sulfonate, p-hydroxymercuribenzoate and ethyl mercurithiosalicylate inhibit CETP.

Connolly et al. (*Biochem. Biophys. Res. Comm.* 223, 42-47 (1996)) describe other cysteine modification reagents as CETP inhibitors. Xia et al. describe 1,3,5-triazines as CETP inhibitors (*Bioorg. Med. Chem. Lett.*, 6, 919-22 (1996)). Bisgaier et al. (*Lipids*, 29, 811-8 (1994)) describe 4-phenyl-5-  
 5 tridecyl-4H-1,2,4-triazole-thiol as a CETP inhibitor. Oomura et al. disclose non-peptidic tetracyclic and hexacyclic phenols as CETP inhibitors in Japanese Patent Application No. 10287662.

Some substituted heteroalkylamine compounds are known. In European Patent Application No. 796846, Schmidt et al. describe 2-aryl-  
 10 substituted pyridines as cholesteryl ester transfer protein inhibitors useful as cardiovascular agents. One substituent at C3 of the pyridine ring can be an hydroxyalkyl group. In European Patent Application No. 801060, Dow and Wright describe heterocyclic derivatives substituted with an aldehyde addition  
 product of an alkylamine to afford 1-hydroxy-1-amines. These are reported to  
 15 be  $\beta$ 3-adrenergic receptor agonists useful for treating diabetes and other disorders. In Great Britain Patent Application No. 2305665, Fisher et al. disclose 3-agonist secondary amino alcohol substituted pyridine derivatives useful for treating several disorders including cholesterol levels and  
 arteriosclerotic diseases. In European Patent Application No. 818448,  
 20 Schmidt et al. describe tetrahydroquinoline derivatives as cholesteryl ester transfer protein inhibitors. European Patent Application No. 818197, Schmek et al. describe pyridines with fused heterocycles as cholesteryl ester transfer protein inhibitors. Brandes et al. in German Patent Application No. 19627430  
 25 describe bicyclic condensed pyridine derivatives as cholesteryl ester transfer protein inhibitors. In WO Patent Application No. 09839299, Muller-Gliemann et al. describe quinoline derivatives as cholesteryl ester transfer protein inhibitors. U.S. Patent 2,700,686, issued to Dickey and Towne, describes N-(2-haloalkyl-2-hydroxyethyl)amines in which the amine is further substituted  
 with either 1 to 2 aliphatic groups or one aromatic group and one aliphatic  
 30 group. U.S. Patent 2,700,686 further describes a process to prepare the N-(2-haloalkyl-2-hydroxyethyl)amines by reacting halogenated-1,2-epoxyalkanes with the corresponding aliphatic amines and N-alkylanilines and their use as dye intermediates.

### SUMMARY OF THE INVENTION

The present invention provides chiral compounds that can be used to inhibit cholesteryl ester transfer protein (CETP) activity and that have the general structure:



5

In another aspect, the present invention includes pharmaceutical compositions comprising a pharmaceutically effective amount of the chiral compounds of this invention and a pharmaceutically acceptable carrier.

In another aspect, this invention relates to methods of using these chiral inhibitors as therapeutic agents in humans to inhibit cholesteryl ester transfer protein (CETP) activity, thereby decreasing the concentrations of low density lipoprotein (LDL) and raising the level of high density lipoprotein (HDL), resulting in a therapeutically beneficial plasma lipid profile. The compounds and methods of this invention can also be used to treat dyslipidemia (hypoalphalipoproteinemia), hyperlipoproteinaemia (chylomicronemia and hyperapobetalipoproteinemia), peripheral vascular disease, hypercholesterolaemia, atherosclerosis, coronary artery disease and other CETP-mediated disorders. The compounds can also be used in prophylactic treatment of subjects who are at risk of developing such disorders. The compounds can be used to lower the risk of atherosclerosis. The compounds of this invention would be also useful in prevention of cerebral vascular accident (CVA) or stroke. Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals,

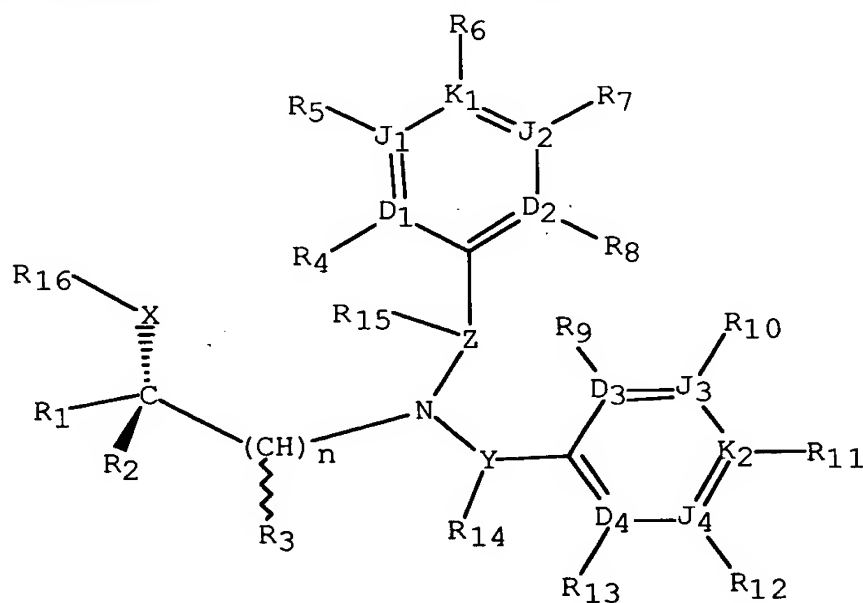


exotic animals and farm animals such as primates, rabbits, pigs, horses, and the like.

5

## DESCRIPTION OF THE INVENTION

The present invention relates to a class of compounds comprising (R)-chiral halogenated 1-substitutedamino-(n+1)-alkanols which are beneficial in the therapeutic and prophylactic treatment of coronary artery disease as given in  
 10 Formula I-H (also referred to herein as generic polycyclic aryl and heteroaryl (R)-chiral halogenated 1-substitutedamino-(n+1)-alkanols):



(I-H)

or a pharmaceutically-acceptable salt thereof, wherein;

15  $n$  is an integer selected from 1 through 4;

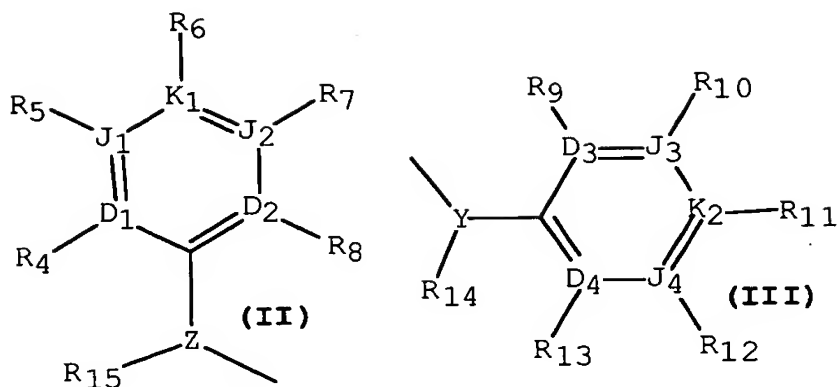
$X$  is oxy;

$R_1$  is selected from the group consisting of haloalkyl, haloalkenyl,

haloalkoxymethyl, and haloalkenyloxymethyl with the proviso that  $R_1$  has a

higher Cahn-Ingold-Prelog stereochemical system ranking than both  $R_2$  and

20  $(CHR_3)_n-N(A)Q$  wherein  $A$  is Formula (II) and  $Q$  is Formula (III);



- R<sub>16</sub> is selected from the group consisting of hydrido, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, alkoxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, aralkoxyalkyl, heteroaralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, monocarboalkoxyalkyl, monocarboalkoxy, dicarboalkoxyalkyl, monocarboxamido, monocyanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, acyl, aroyl, heteroaroyl, heteroaryloxyalkyl, dialkoxyphosphonoalkyl, trialkylsilyl, and a spacer selected from the group consisting of a covalent single bond and a linear spacer moiety having a chain length of 1 to 4 atoms linked to the point of bonding of any aromatic substituent selected from the group consisting of R<sub>4</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>13</sub>, R<sub>14</sub>, and R<sub>15</sub> to form a heterocyclyl ring having from 5 through 10 contiguous members;

- D<sub>1</sub>, D<sub>2</sub>, J<sub>1</sub>, J<sub>2</sub> and K<sub>1</sub> are independently selected from the group consisting of C, N, O, S and covalent bond with the provisos that no more than one of D<sub>1</sub>, D<sub>2</sub>, J<sub>1</sub>, J<sub>2</sub> and K<sub>1</sub> can be a covalent bond, no more than one of D<sub>1</sub>, D<sub>2</sub>, J<sub>1</sub>, J<sub>2</sub> and K<sub>1</sub> can be O, no more than one of D<sub>1</sub>, D<sub>2</sub>, J<sub>1</sub>, J<sub>2</sub> and K<sub>1</sub> can be S, one of D<sub>1</sub>, D<sub>2</sub>, J<sub>1</sub>, J<sub>2</sub> and K<sub>1</sub> must be a covalent bond when two

of  $D_1$ ,  $D_2$ ,  $J_1$ ,  $J_2$  and  $K_1$  are O and S, and no more than four of  $D_1$ ,  $D_2$ ,  $J_1$ ,  $J_2$  and  $K_1$  can be N;

$D_3$ ,  $D_4$ ,  $J_3$ ,  $J_4$  and  $K_2$  are independently selected from the group consisting of C, N, O, S and covalent bond with the provisos that no more than one can be a covalent bond, no more than one of  $D_3$ ,  $D_4$ ,  $J_3$ ,  $J_4$  and  $K_2$  can be O, no more than one of  $D_3$ ,  $D_4$ ,  $J_3$ ,  $J_4$  and  $K_2$  can be S, no more than two of  $D_3$ ,  $D_4$ ,  $J_3$ ,  $J_4$  and  $K_2$  can be O and S, one of  $D_3$ ,  $D_4$ ,  $J_3$ ,  $J_4$  and  $K_2$  must be a covalent bond when two of  $D_3$ ,  $D_4$ ,  $J_3$ ,  $J_4$  and  $K_2$  are O and S, and no more than four of  $D_3$ ,  $D_4$ ,  $J_3$ ,  $J_4$  and  $K_2$  can be N;

10  $R_2$  is hydrido;

$R_2$  can be selected from the group consisting of hydroxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, aralkoxyalkyl, aryloxyalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, 15 halocycloalkyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, perhaloaryl, perhaloaralkyl, perhaloaralkyl, heteroaralkylthioalkyl, monocarboalkoxyalkyl, dicarboalkoxyalkyl, monocyanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, 20 alkylsulfinylalkyl, alkylsulfonylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, cycloalkylsulfinylalkyl, cycloalkylsulfonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, carboxyalkyl, carboalkoxy, carboxamide, carboxamidoalkyl, carboaralkoxy, dicyanoalkyl, carboalkoxycyanoalkyl, dialkoxyphosphonoalkyl, and 25 diaralkoxyphosphonoalkyl with the proviso that  $R_2$  has a lower Cahn-Ingold-

Prelog system ranking than both  $R_1$  and  $(CHR_3)_n-N(A)Q$ ;

$R_3$  is selected from the group consisting of hydrido, hydroxy, halo, cyano, aryloxy, hydroxyalkyl, amino, alkylamino, dialkylamino, acyl,

- acylamido, alkoxy, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, alkoxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aroyl, heteroaroyl, aralkylthioalkyl, heteroaralkylthioalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, haloalkyl, haloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, monocarboalkoxyalkyl, dicarboalkoxyalkyl, monocyanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, arylsulfinylalkyl, arylsulfonylalkyl, cycloalkylsulfinylalkyl, cycloalkylsulfonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, carboxyalkyl, carboalkoxy, carboxamide, carboxamidoalkyl, carboaralkoxy, dialkoxyposphonoalkyl, and diaralkoxyposphonoalkyl with the provisos that  $(\text{CHR}_3)_n\text{-N(A)Q}$  has a lower Cahn-Ingold-Prelog stereochemical system ranking than  $\text{R}_1$  and a higher Cahn-Ingold-Prelog stereochemical system ranking than  $\text{R}_2$ ;
- Y is selected from a group consisting of a covalent single bond,  $(\text{C}(\text{R}_{14})_2)_q$  wherein q is an integer selected from 1 through 2 and  $(\text{CH}(\text{R}_{14}))_g\text{-W-(CH}(\text{R}_{14}))_p$  wherein g and p are integers independently selected from 0 through 1;
- $\text{R}_{14}$  is independently selected from the group consisting of hydrido, hydroxy, halo, cyano, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, acyl, aroyl, heteroaroyl, heteroaryloxyalkyl, sulfhydryl, acylamido, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkylalkoxy, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, monocarboalkoxyalkyl, dicarboalkoxyalkyl, monocyanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, alkylsulfinyl, alkylsulfonyl, haloalkylsulfinyl,

- haloalkylsulfonyl, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, arylsulfonylalkyl, aralkylsulfinyl, aralkylsulfonyl, cycloalkylsulfinyl, cycloalkylsulfonyl, cycloalkylsulfinylalkyl, cycloalkylsulfonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinyl, heteroarylsulfonyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, carboxyalkyl, carboalkoxy, carboxamide, carboxamidoalkyl, carboaralkoxy, dialkoxyposphono, diaralkoxyposphono, dialkoxyposphonoalkyl, diaralkoxyposphonoalkyl, a spacer selected from a moiety having a chain length of 3 to 6 atoms connected to the point of bonding selected from the group consisting of  $R_9$  and  $R_{13}$  to form a ring selected from the group consisting of a cycloalkenyl ring having from 5 through 8 contiguous members and a heterocyclyl ring having from 5 through 8 contiguous members, and a spacer selected from a moiety having a chain length of 2 to 5 atoms connected to the point of bonding selected from the group consisting of  $R_4$  and  $R_8$  to form a heterocyclyl having from 5 through 8 contiguous members with the proviso that, when Y is a covalent bond, an  $R_{14}$  substituent is not attached to Y;

- $R_{14}$  and  $R_{15}$  can be taken together to form a spacer selected from a moiety having a chain length of 2 to 5 atoms to form a heterocyclyl ring having from 5 through 8 contiguous members;

- $R_{14}$  and  $R_{14}$ , when bonded to the different atoms, can be taken together to form a group selected from the group consisting of a covalent bond, alkylene, haloalkylene, and a spacer selected from a group consisting of a moiety having a chain length of 2 to 5 atoms connected to form a ring selected from the group of a saturated cycloalkyl having from 5 through 8 contiguous members, a cycloalkenyl having from 5 through 8 contiguous members, and a heterocyclyl having from 5 through 8 contiguous members;

- $R_{14}$  and  $R_{14}$ , when bonded to the same atom can be taken together to form a group selected from the group consisting of oxo, thiono, alkylene, haloalkylene, and a spacer selected from the group consisting of a moiety having a chain length of 3 to 7 atoms connected to form a ring selected from the group consisting of a cycloalkyl having from 4 through 8 contiguous

members, a cycloalkenyl having from 4 through 8 contiguous members, and a heterocyclyl having from 4 through 8 contiguous members;

W is selected from the group consisting of O, C(O), C(S),

C(O)N(R<sub>14</sub>), C(S)N(R<sub>14</sub>), (R<sub>14</sub>)NC(O), (R<sub>14</sub>)NC(S), S, S(O), S(O)<sub>2</sub>,

- 5 S(O)<sub>2</sub>N(R<sub>14</sub>), (R<sub>14</sub>)NS(O)<sub>2</sub>, and N(R<sub>14</sub>) with the proviso that R<sub>14</sub> is selected from other than halo and cyano;

Z is independently selected from a group consisting of a covalent single bond, (C(R<sub>15</sub>)<sub>2</sub>)<sub>q</sub> wherein q is an integer selected from 1 through 2,

(CH(R<sub>15</sub>))<sub>j</sub>-W-(CH(R<sub>15</sub>))<sub>k</sub> wherein j and k are integers independently

- 10 selected from 0 through 1 with the proviso that, when Z is a covalent single bond, an R<sub>15</sub> substituent is not attached to Z;

R<sub>15</sub> is independently selected, when Z is (C(R<sub>15</sub>)<sub>2</sub>)<sub>q</sub> wherein q is an integer selected from 1 through 2, from the group consisting of hydrido,

- hydroxy, halo, cyano, aryloxy, amino, alkylamino, dialkylamino,  
 15 hydroxyalkyl, acyl, aroyl, heteroaroyl, heteroaryloxyalkyl, sulfhydryl, acylamido, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl,  
 20 cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl,  
 25 monocarboalkoxyalkyl, dicarboalkoxyalkyl, monocyanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, alkylsulfinyl, alkylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, arylsulfonylalkyl, aralkylsulfinyl, aralkylsulfonyl, cycloalkylsulfinyl, cycloalkylsulfonyl, cycloalkylsulfinylalkyl, cycloalkylsulfonylalkyl,  
 30 heteroarylsulfonylalkyl, heteroarylsulfinyl, heteroarylsulfonyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, carboxyalkyl, carboalkoxy, carboxamide, carboxamidoalkyl, carboaralkoxy, dialkoxyphosphono, diaralkoxyphosphono, dialkoxyphosphonoalkyl,

diaralkoxyphosphonoalkyl, a spacer selected from a moiety having a chain length of 3 to 6 atoms connected to the point of bonding selected from the group consisting of  $R_4$  and  $R_8$  to form a ring selected from the group

- 5 consisting of a cycloalkenyl ring having from 5 through 8 contiguous members and a heterocyclyl ring having from 5 through 8 contiguous members, and a spacer selected from a moiety having a chain length of 2 to 5 atoms connected to the point of bonding selected from the group consisting of  $R_9$  and  $R_{13}$  to form a heterocyclyl having from 5 through 8 contiguous members;

- $R_{15}$  and  $R_{15}$ , when bonded to the different atoms, can be taken  
10 together to form a group selected from the group consisting of a covalent bond, alkylene, haloalkylene, and a spacer selected from a group consisting of a moiety having a chain length of 2 to 5 atoms connected to form a ring selected from the group of a saturated cycloalkyl having from 5 through 8 contiguous members, a cycloalkenyl having from 5 through 8 contiguous members, and a  
15 heterocyclyl having from 5 through 8 contiguous members;

- $R_{15}$  and  $R_{15}$ , when bonded to the same atom, can be taken together to form a group selected from the group consisting of oxo, thiono, alkylene, haloalkylene, and a spacer selected from the group consisting of a moiety having a chain length of 3 to 7 atoms connected to form a ring selected from the  
20 group consisting of a cycloalkyl having from 4 through 8 contiguous members, a cycloalkenyl having from 4 through 8 contiguous members, and a heterocyclyl having from 4 through 8 contiguous members;

- $R_{15}$  is independently selected, when Z is  $(CH(R_{15}))_j-W-(CH(R_{15}))_k$  wherein j and k are integers independently selected from 0 through 1, from the  
25 group consisting of hydrido, halo, cyano, aryloxy, carboxyl, acyl, aroyl, heteroaroyl, hydroxyalkyl, heteroaryloxyalkyl, acylamido, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, alkoxyalkyl, heteroaryloxyalkyl, aralkoxyalkyl, heteroaralkoxyalkyl, alkylsulfonylalkyl, alkylsulfinylalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl,  
30 cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl,

heteroaryl, heteroaralkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, monocarboalkoxyalkyl, dicarboalkoxyalkyl, monocyanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, alkylsulfinyl, alkylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, arylsulfonylalkyl, aralkylsulfinyl, aralkylsulfonyl, cycloalkylsulfinyl, cycloalkylsulfonyl, cycloalkylsulfinylalkyl, cycloalkylsulfonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinyl, heteroarylsulfonyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxyalkyl, carboalkoxy, carboxamide, carboxamidoalkyl, carboaralkoxy, dialkoxyposphonoalkyl, diaralkoxyposphonoalkyl, a spacer selected from a linear moiety having a chain length of 3 to 6 atoms connected to the point of bonding selected from the group consisting of R<sub>4</sub> and R<sub>8</sub> to form a ring selected from the group consisting of a cycloalkenyl ring having from 5 through 8 contiguous members and a heterocyclyl ring having from 5 through 8 contiguous members, and a spacer selected from a linear moiety having a chain length of 2 to 5 atoms connected to the point of bonding selected from the group consisting of R<sub>9</sub> and R<sub>13</sub> to form a heterocyclyl ring having from 5 through 8 contiguous members;

R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub>, and R<sub>13</sub> are independently selected from the group consisting of hydrido, carboxy, heteroaralkylthio, heteroaralkoxy, cycloalkylamino, acylalkyl, acylalkoxy, aroylalkoxy, heterocyclyloxy, aralkylaryl, aralkyl, aralkenyl, aralkynyl, heterocyclyl, perhaloaralkyl, aralkylsulfonyl, aralkylsulfonylalkyl, aralkylsulfinyl, aralkylsulfinylalkyl, halocycloalkyl, halocycloalkenyl, cycloalkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, heteroarylamino, N-heteroarylamino-N-alkylamino, heteroaralkyl, heteroarylaminomethyl, haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxylalkyl, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, cycloalkoxyalkyl, cycloalkylalkoxy, cycloalkenyloxyalkyl, cycloalkylenedioxy, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxy, halocycloalkenyloxyalkyl, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, arylthioalkyl, heteroaralkoxyalkyl, alkylsulfinyl, alkylsulfinylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, heteroarylsulfinylalkyl, heteroarylsulfonylalkyl, alkylsulfonyl, alkylsulfonylalkyl,



- haloalkylsulfinylalkyl, haloalkylsulfonylalkyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, heterocyclisulfonyl, heterocyclylthio, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkenyloxy, alkenyloxyalkyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkylalkanoyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, heteroaralkynyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkenyl, heteroarylalkenyl, carboxyalkyl, carboalkoxy, alkoxycarboxamido, alkylamidocarbonylamido, arylamidocarbonylamido, carboalkoxyalkyl, carboalkoxyalkenyl, carboaralkoxy, carboxamido, carboxamidoalkyl, cyano, carbohaloalkoxy, phosphono, phosphonoalkyl, diaralkoxyphosphono, and diaralkoxyphosphonoalkyl with the proviso that there are one to five non-hydrido ring substituents  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$ , and  $R_8$  present, that there are one to five non-hydrido ring substituents  $R_9$ ,  $R_{10}$ ,  $R_{11}$ ,  $R_{12}$ , and  $R_{13}$  present, and  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$ ,  $R_8$ ,  $R_9$ ,  $R_{10}$ ,  $R_{11}$ ,  $R_{12}$ , and  $R_{13}$  are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;
- $R_4$  and  $R_5$ ,  $R_5$  and  $R_6$ ,  $R_6$  and  $R_7$ ,  $R_7$  and  $R_8$ ,  $R_9$  and  $R_{10}$ ,  $R_{10}$  and  $R_{11}$ ,  $R_{11}$  and  $R_{12}$ , and  $R_{12}$  and  $R_{13}$  can be independently selected to form spacer pairs wherein a spacer pair is taken together to form a linear moiety having from 3 through 6 contiguous atoms connecting the points of bonding of said spacer pair members to form a ring selected from the group consisting of a cycloalkenyl ring having 5 through 8 contiguous members, a partially saturated heterocyclyl ring having 5 through 8 contiguous members, a heteroaryl ring having 5 through 6 contiguous members, and an aryl with the provisos that no

more than one of the group consisting of spacer pairs R<sub>4</sub> and R<sub>5</sub>, R<sub>5</sub> and R<sub>6</sub>, R<sub>6</sub> and R<sub>7</sub>, and R<sub>7</sub> and R<sub>8</sub>, can be used at the same time and that no more than one of the group consisting of spacer pairs R<sub>9</sub> and R<sub>10</sub>, R<sub>10</sub> and R<sub>11</sub>, R<sub>11</sub> and R<sub>12</sub>, and R<sub>12</sub> and R<sub>13</sub> can be used at the same time;

5           R<sub>4</sub> and R<sub>9</sub>, R<sub>4</sub> and R<sub>13</sub>, R<sub>8</sub> and R<sub>9</sub>, and R<sub>8</sub> and R<sub>13</sub> can be independently selected to form a spacer pair wherein said spacer pair is taken together to form a linear moiety wherein said linear moiety forms a ring selected from the group consisting of a partially saturated heterocyclyl ring having from 5 through 8 contiguous members and a heteroaryl ring having  
10           from 5 through 6 contiguous members with the proviso that no more than one of the group consisting of spacer pairs R<sub>4</sub> and R<sub>9</sub>, R<sub>4</sub> and R<sub>13</sub>, R<sub>8</sub> and R<sub>9</sub>, and R<sub>8</sub> and R<sub>13</sub> can be used at the same time;

              R<sub>5</sub> and R<sub>10</sub>, R<sub>5</sub> and R<sub>12</sub>, R<sub>7</sub> and R<sub>10</sub>, and R<sub>7</sub> and R<sub>12</sub> can be independently selected to form a spacer pair wherein said spacer pair is taken  
15           together to form a linear moiety wherein said linear moiety forms a C8 to C13 heterocyclyl ring having from 8 through 13 contiguous members with the proviso that no more than one of the group consisting of spacer pairs R<sub>5</sub> and R<sub>10</sub>, R<sub>5</sub> and R<sub>12</sub>, R<sub>7</sub> and R<sub>10</sub>, and R<sub>7</sub> and R<sub>12</sub> can be used at the same time.

20

In a another embodiment of compounds of Formula I-H,

              D<sub>1</sub>, D<sub>2</sub>, J<sub>1</sub>, J<sub>2</sub> and K<sub>1</sub> are each carbon with the proviso that at least one of D<sub>3</sub>, D<sub>4</sub>, J<sub>3</sub>, J<sub>4</sub> and K<sub>2</sub> is selected from the group consisting of O, S, and N, wherein D<sub>3</sub>, D<sub>4</sub>, J<sub>3</sub>, J<sub>4</sub> and K<sub>2</sub> are independently selected from the  
25           group consisting of C, N, O, S and covalent bond with the provisos that no more than one of D<sub>3</sub>, D<sub>4</sub>, J<sub>3</sub>, J<sub>4</sub> and K<sub>2</sub> can be a covalent bond, no more than one of D<sub>3</sub>, D<sub>4</sub>, J<sub>3</sub>, J<sub>4</sub> and K<sub>2</sub> can be O, no more than one of D<sub>3</sub>, D<sub>4</sub>, J<sub>3</sub>, J<sub>4</sub>

and  $K_2$  can be S, one of  $D_3, D_4, J_3, J_4$  and  $K_2$  must be a covalent bond when two of  $D_3, D_4, J_3, J_4$  and  $K_2$  are O and S, and no more than four of  $D_3, D_4, J_3, J_4$  and  $K_2$  can be N;

$D_1, D_2, J_1, J_2$  and  $K_1$  can be selected from the group consisting of C,

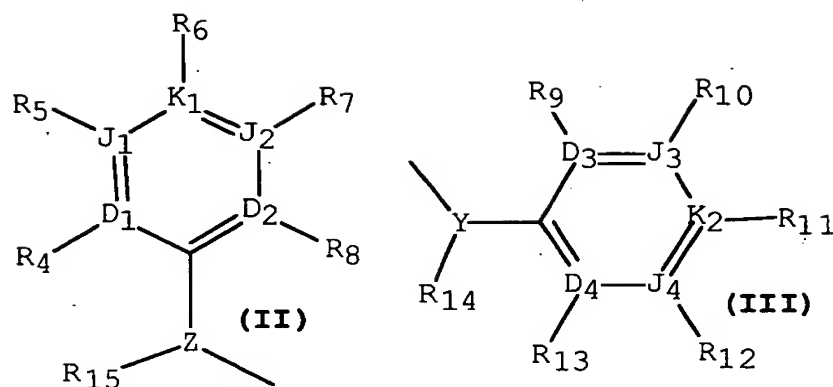
- 5 O, S, N and covalent bond with the provisos that  $D_3, D_4, J_3, J_4$  and  $K_2$  are each carbon and at least one of  $D_1, D_2, J_1, J_2$  and  $K_1$  is selected from the group consisting of O, S, and N wherein, when  $D_1, D_2, J_1, J_2$  and  $K_1$  are selected from the group consisting of C, O, S, covalent bond, and N, no more than one of  $D_1, D_2, J_1, J_2$  and  $K_1$  can be a covalent bond, no more than one
- 10 of  $D_1, D_2, J_1, J_2$  and  $K_1$  can be O, no more than one of  $D_1, D_2, J_1, J_2$  and  $K_1$  can be S, one of  $D_1, D_2, J_1, J_2$  and  $K_1$  must be a covalent bond when two of  $D_1, D_2, J_1, J_2$  and  $K_1$  are O and S, and no more than four of  $D_1, D_2, J_1, J_2$  and  $K_1$  can be N;

$n$  is an integer selected from 1 through 4;

- 15 X is oxy;

$R_{16}$  is selected from the group consisting of hydrido, acyl, aroyl, and trialkylsilyl;

- $R_1$  is selected from the group consisting of haloalkyl, haloalkenyl, haloalkoxymethyl, and haloalkenyloxymethyl with the proviso that  $R_1$  has a
- 20 higher Cahn-Ingold-Prelog stereochemical system ranking than both  $R_2$  and  $(CHR_3)_n-N(A)Q$  wherein A is Formula (II) and Q is Formula (III);



$R_2$  is hydrido;

$R_2$  can be selected from the group consisting of aryl, aralkyl, alkyl,

- 5 alkenyl, alkenyloxyalkyl, haloalkyl, haloalkenyl, halocycloalkyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, dicyanoalkyl, and carboalkoxycyanoalkyl with the proviso that  $R_2$  has a lower Cahn-Ingold-

Prelog system ranking than both  $R_1$  and  $(CHR_3)_n-N(A)Q$ ;

- 10  $R_3$  is selected from the group consisting of hydrido, hydroxy, cyano, aryl, aralkyl, acyl, alkoxy, alkyl, alkenyl, alkoxyalkyl, heteroaryl, alkenyloxyalkyl, haloalkyl, haloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, monocyanoalkyl, dicyanoalkyl, carboxamide, and carboxamidoalkyl with the provisos that  $(CHR_3)_n-N(A)Q$  has a lower Cahn-

- 15 Ingold-Prelog stereochemical system ranking than  $R_1$  and a higher Cahn-

Ingold-Prelog stereochemical system ranking than  $R_2$ ;

Y is selected from the group consisting of covalent single bond and  $(C(R_{14})_2)_q$  wherein q is an integer selected from 1 through 2;

$R_{14}$  is selected from the group consisting of hydrido, cyano,

- 20 hydroxyalkyl, acyl, alkoxy, alkyl, alkenyl, alkoxyalkyl, haloalkyl, haloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, monocyanoalkyl, dicyanoalkyl, carboxamide, and carboxamidoalkyl;

Z is selected from the group consisting of covalent single bond,  
 $(C(R_{15})_2)_q$  wherein q is an integer selected from 1 through 2, and  
 $(CH(R_{15}))_j-W-(CH(R_{15}))_k$  wherein j and k are integers independently  
 selected from 0 through 1;

5 W is oxy;

$R_{15}$  is selected from the group consisting of hydrido, cyano,  
 hydroxyalkyl, acyl, alkoxy, alkyl, alkenyl, alkoxyalkyl, haloalkyl,  
 haloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl,  
 monocyanoalkyl, dicyanoalkyl, carboxamide, and carboxamidoalkyl;

10  $R_4$ ,  $R_8$ ,  $R_9$ , and  $R_{13}$  are independently selected from the group  
 consisting of hydrido, halo, haloalkyl, and alkyl ;

$R_5$ ,  $R_6$ ,  $R_7$ ,  $R_{10}$ ,  $R_{11}$ , and  $R_{12}$  are independently selected from the  
 group consisting of hydrido, carboxy, heteroaralkylthio, heteroarylsulfonyl,  
 heteroaralkoxy, cycloalkylamino, acylalkyl, acylalkoxy, aroylalkoxy,  
 15 heterocyclyloxy, aralkylaryl, aralkyl, aralkenyl, aralkynyl, heterocyclyl,  
 haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, cycloalkoxy,  
 cycloalkylalkoxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio,  
 arylamino, aralkylamino, arylthio, arylthioalkyl, alkylsulfonyl,  
 alkylsulfonamido, monoarylamidosulfonyl, arylsulfonyl, heteroarylthio,  
 20 heterocyclylsulfonyl, heterocyclylthio, alkanoyl, alkenoyl, aroyl, alkyl,  
 alkenyl, alkynyl, alkenyloxy, alkylenedioxy, haloalkylenedioxy, cycloalkyl,  
 cycloalkylalkanoyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl,  
 hydroxyalkyl, aryl, aryloxy, aralkoxy, saturated heterocyclyl, heteroaryl,  
 heteroaryloxy, heteroaryloxyalkyl, heteroaralkyl, carboalkoxy,  
 25 alkoxycarboxamido, alkylamidocarbonylamido, arylamidocarbonylamido,  
 carboalkoxyalkyl, carboalkoxyalkenyl, carboxamido, carboxamidoalkyl, and  
 cyano;

$R_4$  and  $R_5$ ,  $R_5$  and  $R_6$ ,  $R_6$  and  $R_7$ ,  $R_7$  and  $R_8$ ,  $R_9$  and  $R_{10}$ ,  $R_{10}$  and  
 $R_{11}$ ,  $R_{11}$  and  $R_{12}$ , and  $R_{12}$  and  $R_{13}$  spacer pairs can be independently  
 30 selected from the group consisting of alkylene, alkenylene, alkylenedioxy,  
 aralkylene, diacyl, haloalkylene, and aryloxylylene with the provisos that no

more than one of the group consisting of spacer pairs R<sub>4</sub> and R<sub>5</sub>, R<sub>5</sub> and R<sub>6</sub>, R<sub>6</sub> and R<sub>7</sub>, and R<sub>7</sub> and R<sub>8</sub> can be used at the same time and that no more than one of the group consisting of spacer pairs R<sub>9</sub> and R<sub>10</sub>, R<sub>10</sub> and R<sub>11</sub>, R<sub>11</sub> and R<sub>12</sub>, and R<sub>12</sub> and R<sub>13</sub> can be used at the same time.

5

In an even more specific embodiment of compounds Formula I-H,

D<sub>1</sub>, D<sub>2</sub>, J<sub>1</sub>, J<sub>2</sub> and K<sub>1</sub> are each carbon;

10 D<sub>3</sub>, D<sub>4</sub>, J<sub>3</sub>, J<sub>4</sub> and K<sub>2</sub> are independently selected from the group consisting of C, N, O, S and covalent bond with the provisos that at least one of D<sub>3</sub>, D<sub>4</sub>, J<sub>3</sub>, J<sub>4</sub> and K<sub>2</sub> is selected from the group consisting of O, S, and N, wherein no more than one of D<sub>3</sub>, D<sub>4</sub>, J<sub>3</sub>, J<sub>4</sub> and K<sub>2</sub> can be a covalent bond, no more than one of D<sub>3</sub>, D<sub>4</sub>, J<sub>3</sub>, J<sub>4</sub> and K<sub>2</sub> can be O, no more than one of D<sub>3</sub>, D<sub>4</sub>, J<sub>3</sub>, J<sub>4</sub> and K<sub>2</sub> can be S, one of D<sub>3</sub>, D<sub>4</sub>, J<sub>3</sub>, J<sub>4</sub> and K<sub>2</sub> must be a covalent bond when two of D<sub>3</sub>, D<sub>4</sub>, J<sub>3</sub>, J<sub>4</sub> and K<sub>2</sub> are O and S, and no more  
15 than four of D<sub>3</sub>, D<sub>4</sub>, J<sub>3</sub>, J<sub>4</sub> and K<sub>2</sub> can be N;

n is an integer selected from 1 to 3;

X is oxy;

R<sub>1</sub> is selected from the group consisting of trifluoromethyl, 1,1,2,2-tetrafluoroethoxymethyl, trifluoromethoxymethyl, chloromethyl, 20 fluoromethyl, difluoromethyl, chlorodifluoromethyl, pentafluoroethyl, 2,2,3,3,3-pentafluoropropyl, and heptafluoropropyl;

R<sub>16</sub> is selected from the group consisting of acetyl, benzoyl, dimethyl *tert*-butylsilyl, hydrido, and trimethylsilyl;

R<sub>2</sub> is hydrido;

25 R<sub>2</sub> can be selected from the group consisting of hydrido, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, vinyl, phenyl,

4-trifluoromethylphenyl, 1,1,2,2-tetrafluoroethoxymethyl, chloromethyl, trifluoromethoxymethyl, fluoromethyl, difluoromethyl, 2,2,3,3,3-pentafluoropropyl, and pentafluorophenoxymethyl with the proviso that  $R_2$  has a lower Cahn-Ingold-Prelog system ranking than both  $R_1$  and  $(CHR_3)_n$ -

5 N(A)Q;

$R_3$  is selected from the group consisting of hydrido, hydroxy, cyano, acetyl, methoxy, ethoxy, methyl, ethyl, propyl, vinyl, phenyl, methoxymethyl, 4-trifluoromethylphenyl, trifluoromethyl, 1,1,2,2-tetrafluoroethoxymethyl, trifluoromethoxymethyl, chloromethyl, fluoromethyl, difluoromethyl, 10 chlorodifluoromethyl, pentafluoroethyl, 2,2,3,3,3-pentafluoropropyl, heptafluoropropyl, pentafluorophenyl, and pentafluorophenoxymethyl with the provisos that  $(CHR_3)_n$ -N(A)Q has a lower Cahn-Ingold-Prelog stereochemical system ranking than  $R_1$  and a higher Cahn-Ingold-Prelog stereochemical system ranking than  $R_2$ .

15

In another even more specific embodiment of compounds Formula I-H,  $D_3$ ,  $D_4$ ,  $J_3$ ,  $J_4$  and  $K_2$  are each carbon;

$D_1$ ,  $D_2$ ,  $J_1$ ,  $J_2$  and  $K_1$  are independently selected from the group consisting of C, N, O, S and covalent bond with the provisos that at least one 20 of  $D_1$ ,  $D_2$ ,  $J_1$ ,  $J_2$  and  $K_1$  is selected from the group consisting of O, S, and N, wherein no more than one of  $D_1$ ,  $D_2$ ,  $J_1$ ,  $J_2$  and  $K_1$  can be a covalent bond, no more than one of  $D_1$ ,  $D_2$ ,  $J_1$ ,  $J_2$  and  $K_1$  can be O, no more than one of  $D_1$ ,  $D_2$ ,  $J_1$ ,  $J_2$  and  $K_1$  can be S, one of  $D_1$ ,  $D_2$ ,  $J_1$ ,  $J_2$  and  $K_1$  must be a covalent bond when two of  $D_1$ ,  $D_2$ ,  $J_1$ ,  $J_2$  and  $K_1$  are O and S, and no more 25 than four of  $D_1$ ,  $D_2$ ,  $J_1$ ,  $J_2$  and  $K_1$  can be N;

$n$  is an integer selected from 1 to 3;

X is oxy;

$R_1$  is selected from the group consisting of trifluoromethyl, 1,1,2,2-tetrafluoroethoxymethyl, trifluoromethoxymethyl, chloromethyl, fluoromethyl, difluoromethyl, chlorodifluoromethyl, pentafluoroethyl, 2,2,3,3,3-pentafluoropropyl, and heptafluoropropyl;

- 5  $R_{16}$  is selected from the group consisting of acetyl, benzoyl, dimethyl *tert*-butylsilyl, hydrido, and trimethylsilyl;

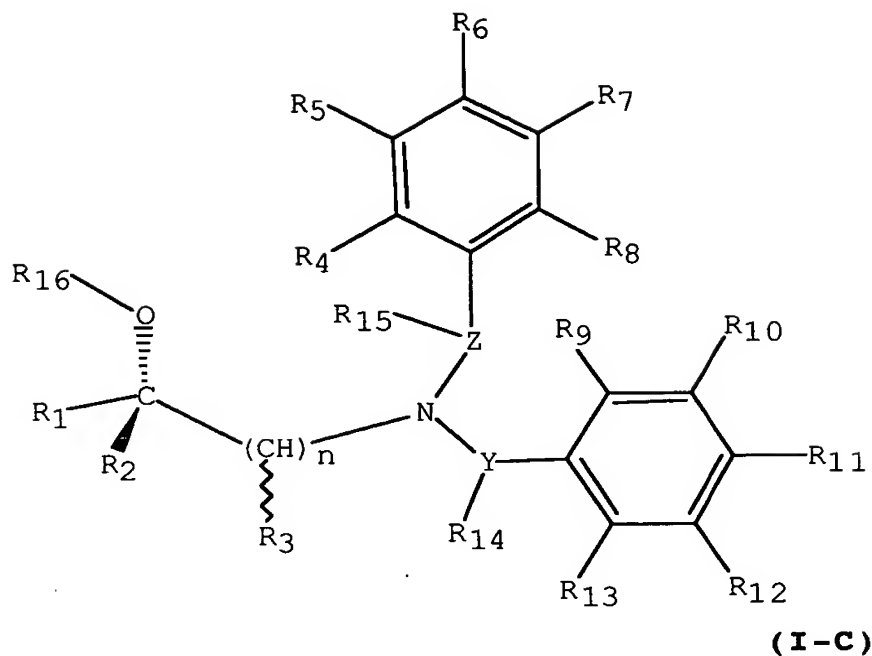
$R_2$  is hydrido;

- $R_2$  can be selected from the group consisting of hydrido, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, vinyl, phenyl,  
10 4-trifluoromethylphenyl, 1,1,2,2-tetrafluoroethoxymethyl, chloromethyl, trifluoromethoxymethyl, fluoromethyl, difluoromethyl, 2,2,3,3,3-pentafluoropropyl, and pentafluorophenoxymethyl with the proviso that  $R_2$  has a lower Cahn-Ingold-Prelog system ranking than both  $R_1$  and  $(CHR_3)_n-N(A)Q$ ;

- 15  $R_3$  is selected from the group consisting of hydrido, hydroxy, cyano, acetyl, methoxy, ethoxy, methyl, ethyl, propyl, vinyl, phenyl, methoxymethyl, 4-trifluoromethylphenyl, trifluoromethyl, 1,1,2,2-tetrafluoroethoxymethyl, trifluoromethoxymethyl, chloromethyl, fluoromethyl, difluoromethyl, chlorodifluoromethyl, pentafluoroethyl, 2,2,3,3,3-pentafluoropropyl,  
20 heptafluoropropyl, pentafluorophenyl, and pentafluorophenoxymethyl with the provisos that  $(CHR_3)_n-N(A)Q$  has a lower Cahn-Ingold-Prelog stereochemical system ranking than  $R_1$  and a higher Cahn-Ingold-Prelog stereochemical system ranking than  $R_2$ .

- 25 In a preferred embodiment of compounds of Formula I-H, the compounds correspond to the Formula I-C (also referred to herein as phenyl (R)-chiral halogenated 1-substitutedamino-(n+1)-alkanols):





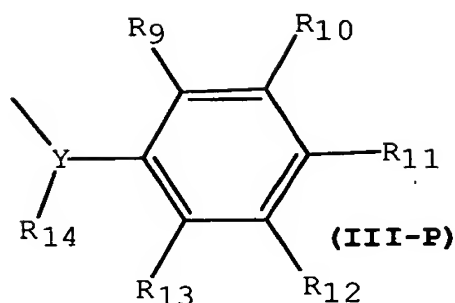
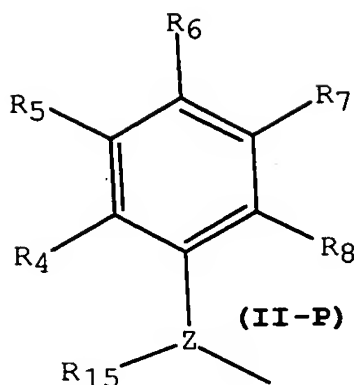
or a pharmaceutically acceptable salt thereof, wherein;

$n$  is an integer selected from 1 through 4;

- 5  $R_{16}$  is selected from the group consisting of hydrido, alkyl, acyl, aroyl, heteroaroyl, trialkylsilyl, and a spacer selected from the group consisting of a covalent single bond and a linear spacer moiety having a chain length of 1 to 4 atoms linked to the point of bonding of any aromatic substituent selected from the group consisting of  $R_4$ ,  $R_8$ ,  $R_9$ , and  $R_{13}$  to form a heterocyclyl ring
- 10 having from 5 through 10 contiguous members with the proviso that said linear spacer moiety is other than covalent single bond when  $R_2$  is alkyl;

$R_1$  is selected from the group consisting of haloalkyl, haloalkenyl, haloalkoxymethyl, and haloalkenyloxymethyl with the proviso that  $R_1$  has a higher Cahn-Ingold-Prelog stereochemical system ranking than both  $R_2$  and

- 15  $(CHR_3)_n-N(Ap)Qp$  wherein Ap is Formula (II-P) and Qp is Formula (III-P);



$R_2$  is hydrido;

$R_2$  can be selected from the group consisting of aryl, aralkyl, alkyl,

- 5    alkenyl, alkenyloxyalkyl, haloalkyl, haloalkenyl, halocycloalkyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, dicyanoalkyl, and carboalkoxycyanoalkyl with the proviso that  $R_2$  has a lower Cahn-Ingold-

Prelog system ranking than both  $R_1$  and  $(CHR_3)_n-N(Ap)Qp$ ;

- 10         $R_3$  is selected from the group consisting of hydrido, hydroxy, cyano, aryl, aralkyl, acyl, alkoxy, alkyl, alkenyl, alkoxyalkyl, heteroaryl, alkenyloxyalkyl, haloalkyl, haloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, monocyanoalkyl, dicyanoalkyl, carboxamide, and carboxamidoalkyl with the provisos that  $(CHR_3)_n-N(Ap)Qp$  has a lower Cahn-

- 15    Ingold-Prelog stereochemical system ranking than  $R_1$  and a higher Cahn-

Ingold-Prelog stereochemical system ranking than  $R_2$ ;

$Y$  is selected from the group consisting of covalent single bond and  $(C(R_{14})_2)_q$  wherein  $q$  is an integer selected from 1 through 2;

$R_{14}$  is selected from the group consisting of hydrido, hydroxy, cyano,

- 20    hydroxyalkyl, acyl, alkoxy, alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkyl, haloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl,

monocarboalkoxyalkyl, monocyanoalkyl, dicyanoalkyl,  
carboalkoxycyanoalkyl, carboalkoxy, carboxamide, carboxamidoalkyl;

Z is selected from the group consisting of covalent single bond,

$(C(R_{15})_2)_q$  wherein q is an integer selected from 1 through 2, and

- 5  $(CH(R_{15}))_j-W-(CH(R_{15}))_k$  wherein j and k are integers independently selected from 0 through 1;

W is selected from the group consisting of O, C(O), C(S),

C(O)N(R<sub>14</sub>), C(S)N(R<sub>14</sub>), (R<sub>14</sub>)NC(O), (R<sub>14</sub>)NC(S), S, S(O), S(O)<sub>2</sub>,

S(O)<sub>2</sub>N(R<sub>14</sub>), (R<sub>14</sub>)NS(O)<sub>2</sub>, and N(R<sub>14</sub>) with the proviso that R<sub>14</sub> is other

- 10 than cyano;

R<sub>15</sub> is selected from the group consisting of hydrido, cyano,

hydroxyalkyl, acyl, alkoxy, alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkyl,

haloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl,

monocarboalkoxyalkyl, monocyanoalkyl, dicyanoalkyl,

- 15 carboalkoxycyanoalkyl, carboalkoxy, carboxamide, and carboxamidoalkyl;

R<sub>4</sub>, R<sub>8</sub>, R<sub>9</sub>, and R<sub>13</sub> are independently selected from the group consisting of hydrido, halo, haloalkyl, and alkyl ;

R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>10</sub>, R<sub>11</sub>, and R<sub>12</sub> are independently selected from the group consisting of hydrido, carboxy, heteroaralkylthio, heteroaralkoxy,

- 20 cycloalkylamino, acylalkyl, acylalkoxy, aroylalkoxy, heterocyclyloxy,

aralkylaryl, aralkyl, aralkenyl, aralkynyl, heterocyclyl, perhaloaralkyl,

aralkylsulfonyl, aralkylsulfonylalkyl, aralkylsulfinyl, aralkylsulfinylalkyl,

halocycloalkyl, halocycloalkenyl, cycloalkylsulfinyl, cycloalkylsulfinylalkyl,

cycloalkylsulfonyl, cycloalkylsulfonylalkyl, heteroaryl amino, N-

- 25 heteroaryl amino-N-alkyl amino, heteroaryl aminoalkyl, haloalkylthio,

alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxylalkyl, heteroaralkoxy,

cycloalkoxy, cycloalkenyloxy, cycloalkoxyalkyl, cycloalkylalkoxy,

cycloalkenyloxyalkyl, cycloalkylenedioxy, halocycloalkoxy,

halocycloalkoxyalkyl, halocycloalkenyloxy, halocycloalkenyloxyalkyl,

- 30 hydroxy, amino, thio, nitro, lower alkyl amino, alkylthio, alkylthioalkyl,

aryl amino, aralkyl amino, arylthio, arylthioalkyl, heteroaralkoxyalkyl,

alkylsulfinyl, alkylsulfinylalkyl, arylsulfinylalkyl, arylsulfonylalkyl,

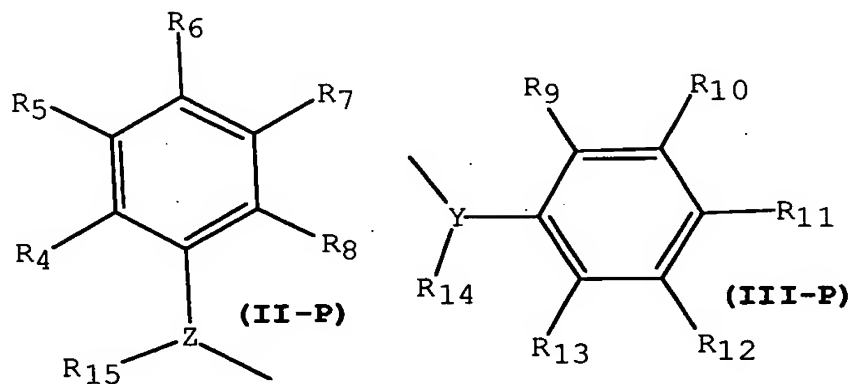
- heteroarylsulfinylalkyl, heteroarylsulfonylalkyl, alkylsulfonyl, alkylsulfonylalkyl, haloalkylsulfinylalkyl, haloalkylsulfonylalkyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl,
- 5 arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, heterocyclylsulfonyl, heterocyclylthio, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkenyloxy, alkenyloxyalkyl, alkylenedioxy, haloalkylenedioxy,
- 10 cycloalkyl, cycloalkylalkanoyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, heteroaralkynyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl,
- 15 heteroaralkyl, arylalkenyl, heteroarylalkenyl, carboxyalkyl, carboalkoxy, alkoxycarboxamido, alkylamidocarbonylamido, arylamidocarbonylamido, carboalkoxyalkyl, carboalkoxyalkenyl, carboaralkoxy, carboxamido, carboxamidoalkyl, cyano, carbohaloalkoxy, phosphono, phosphonoalkyl, diaralkoxyphosphono, and diaralkoxyphosphonoalkyl;
- 20  $R_4$  and  $R_5$ ,  $R_5$  and  $R_6$ ,  $R_6$  and  $R_7$ ,  $R_7$  and  $R_8$ ,  $R_9$  and  $R_{10}$ ,  $R_{10}$  and  $R_{11}$ ,  $R_{11}$  and  $R_{12}$ , and  $R_{12}$  and  $R_{13}$  can be independently selected to form spacer pairs wherein a spacer pair is taken together to form a linear moiety having from 3 through 6 contiguous atoms connecting the points of bonding of said spacer pair members to form a ring selected from the group consisting of a
- 25 cycloalkenyl ring having 5 through 8 contiguous members, a partially saturated heterocyclyl ring having 5 through 8 contiguous members, a heteroaryl ring having 5 through 6 contiguous members, and an aryl with the provisos that no more than one of the group consisting of spacer pairs  $R_4$  and  $R_5$ ,  $R_5$  and  $R_6$ ,  $R_6$  and  $R_7$ , and  $R_7$  and  $R_8$ , can be used at the same time and that no more than
- 30 one of the group consisting of spacer pairs  $R_9$  and  $R_{10}$ ,  $R_{10}$  and  $R_{11}$ ,  $R_{11}$  and  $R_{12}$ , and  $R_{12}$  and  $R_{13}$  can be used at the same time.

In a preferred embodiment of compounds of Formula I-C,

$n$  is an integer selected from 1 through 4;

$R_{16}$  is selected from the group consisting of hydrido, acyl, aroyl, and  
5 trialkylsilyl;

$R_1$  is selected from the group consisting of haloalkyl, haloalkenyl,  
haloalkoxymethyl, and haloalkenyloxymethyl with the proviso that  $R_1$  has a  
higher Cahn-Ingold-Prelog stereochemical system ranking than both  $R_2$  and  
(CHR<sub>3</sub>)<sub>n</sub>-N(Ap)Qp wherein Ap is Formula (II-P) and Qp is Formula (III-P);



$R_2$  is hydrido;

$R_2$  can be selected from the group consisting of aryl, aralkyl, alkyl,  
alkenyl, alkenyloxyalkyl, haloalkyl, haloalkenyl, halocycloalkyl, haloalkoxy,  
haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl,  
15 perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, dicyanoalkyl, and  
carboalkoxycyanoalkyl with the proviso that  $R_2$  has a lower Cahn-Ingold-  
Prelog system ranking than both  $R_1$  and (CHR<sub>3</sub>)<sub>n</sub>-N(Ap)Qp;

$R_3$  is selected from the group consisting of hydrido, hydroxy, cyano,  
aryl, aralkyl, acyl, alkoxy, alkyl, alkenyl, alkoxyalkyl, heteroaryl,  
20 alkenyloxyalkyl, haloalkyl, haloalkenyl, haloalkoxy, haloalkoxyalkyl,  
haloalkenyloxyalkyl, monocyanoalkyl, dicyanoalkyl, carboxamide, and

carboxamidoalkyl with the provisos that  $(\text{CHR}_3)_n\text{-N}(\text{Ap})\text{Qp}$  has a lower Cahn-Ingold-Prelog stereochemical system ranking than  $\text{R}_1$  and a higher Cahn-Ingold-Prelog stereochemical system ranking than  $\text{R}_2$ ;

Y is selected from the group consisting of covalent single bond and

5  $(\text{C}(\text{R}_{14})_2)_q$  wherein q is an integer selected from 1 through 2;

$\text{R}_{14}$  is selected from the group consisting of hydrido, cyano, hydroxyalkyl, acyl, alkoxy, alkyl, alkenyl, alkoxyalkyl, haloalkyl, haloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, monocyanoalkyl, dicyanoalkyl, carboxamide, and carboxamidoalkyl;

10 Z is selected from the group consisting of covalent single bond,

$(\text{C}(\text{R}_{15})_2)_q$  wherein q is an integer selected from 1 through 2, and

$(\text{CH}(\text{R}_{15}))_j\text{-W}(\text{CH}(\text{R}_{15}))_k$  wherein j and k are integers independently selected from 0 through 1;

W is oxy;

15  $\text{R}_{15}$  is selected from the group consisting of hydrido, cyano,

hydroxyalkyl, acyl, alkoxy, alkyl, alkenyl, alkoxyalkyl, haloalkyl, haloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, monocyanoalkyl, dicyanoalkyl, carboxamide, and carboxamidoalkyl;

$\text{R}_4$ ,  $\text{R}_8$ ,  $\text{R}_9$ , and  $\text{R}_{13}$  are independently selected from the group  
20 consisting of hydrido, halo, haloalkyl, and alkyl ;

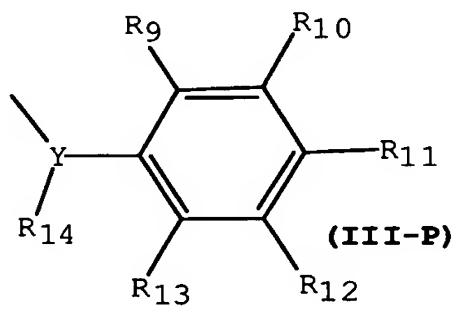
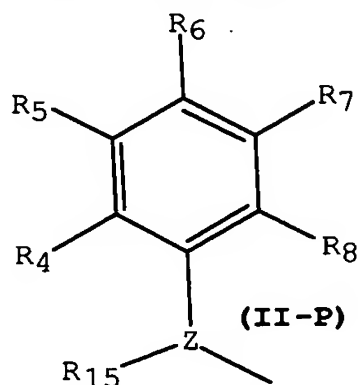
$\text{R}_5$ ,  $\text{R}_6$ ,  $\text{R}_7$ ,  $\text{R}_{10}$ ,  $\text{R}_{11}$ , and  $\text{R}_{12}$  are independently selected from the group consisting of hydrido, carboxy, heteroaralkylthio, heteroarylsulfonyl, heteroaralkoxy, cycloalkylamino, acylalkyl, acylalkoxy, aroylalkoxy, heterocyclyloxy, aralkylaryl, aralkyl, aralkenyl, aralkynyl, heterocyclyl, 25 haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, cycloalkoxy, cycloalkylalkoxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, arylamino, aralkylamino, arylthio, arylthioalkyl, alkylsulfonyl, alkylsulfonamido, monoarylamidosulfonyl, arylsulfonyl, heteroarylthio, heterocyclylsulfonyl, heterocyclylthio, alkanoyl, alkenoyl, aroyl, alkyl, 30 alkenyl, alkynyl, alkenyloxy, alkylenedioxy, haloalkylenedioxy, cycloalkyl,

- cycloalkylalkanoyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyalkyl, aryl, alkyl, aryloxy, aralkoxy, saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, carboalkoxy, alkoxycarboxamido, alkylamidocarbonylamido, arylamidocarbonylamido, carboalkoxyalkyl, carboalkoxyalkenyl, carboxamido, carboxamidoalkyl, and cyano;

- $R_4$  and  $R_5$ ,  $R_5$  and  $R_6$ ,  $R_6$  and  $R_7$ ,  $R_7$  and  $R_8$ ,  $R_9$  and  $R_{10}$ ,  $R_{10}$  and  $R_{11}$ ,  $R_{11}$  and  $R_{12}$ , and  $R_{12}$  and  $R_{13}$  spacer pairs can be independently selected from the group consisting of alkylene, alkenylene, alkylendioxy, aralkylene, diacyl, haloalkylene, and aryloxylylene with the provisos that no more than one of the group consisting of spacer pairs  $R_4$  and  $R_5$ ,  $R_5$  and  $R_6$ ,  $R_6$  and  $R_7$ , and  $R_7$  and  $R_8$  can be used at the same time and that no more than one of the group consisting of spacer pairs  $R_9$  and  $R_{10}$ ,  $R_{10}$  and  $R_{11}$ ,  $R_{11}$  and  $R_{12}$ , and  $R_{12}$  and  $R_{13}$  can be used at the same time.

- In a more preferred embodiment of compounds of Formula I-C,  $n$  is an integer selected from 1 through 2;

- $R_1$  is selected from the group consisting of haloalkyl and haloalkoxymethyl with the proviso that  $R_1$  has a higher Cahn-Ingold-Prelog stereochemical system ranking than both  $R_2$  and  $(CHR_3)_n-N(Ap)Qp$  wherein  $Ap$  is Formula (II-P) and  $Qp$  is Formula (III-P);



$R_{16}$  is hydrido;

$R_2$  is selected from the group consisting of hydrido, aryl, alkyl, alkenyl, haloalkyl, haloalkoxy, haloalkoxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, and heteroaryl with the proviso that  $R_2$  has a lower Cahn-

- 5 Ingold-Prelog system ranking than both  $R_1$  and  $(CHR_3)_n-N(Ap)Qp$ ;

$R_3$  is selected from the group consisting of hydrido, aryl, alkyl, alkenyl, haloalkyl, and haloalkoxyalkyl with the provisos that  $(CHR_3)_n-N(Ap)Qp$  has a lower Cahn-Ingold-Prelog stereochemical system ranking than  $R_1$  and a higher Cahn-Ingold-Prelog stereochemical system ranking than  $R_2$ ;

- 10 Y is selected from the group consisting of a covalent single bond and alkylene;

Z is selected from the group consisting of a covalent single bond and alkylene;

- 15  $R_{14}$  is selected from the group consisting of hydrido, alkyl, and haloalkyl;

$R_{15}$  is selected from the group consisting of hydrido, alkyl, and haloalkyl;

$R_4$ ,  $R_8$ ,  $R_9$ , and  $R_{13}$  are independently selected from the group consisting of hydrido and halo;

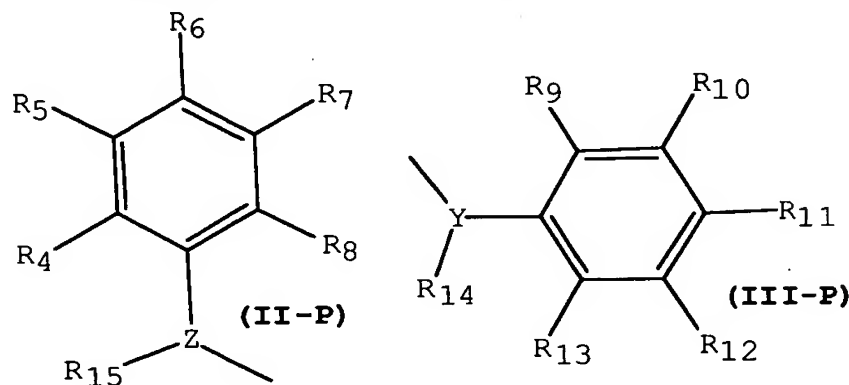
- 20  $R_5$ ,  $R_6$ ,  $R_7$ ,  $R_{10}$ ,  $R_{11}$ , and  $R_{12}$  are independently selected from the group consisting of hydrido, alkyl, halo, haloalkyl, haloalkoxy, aryl, alkylthio, arylamino, arylthio, aroyl, arylsulfonyl, aryloxy, aralkoxy, heteroaryloxy, alkoxy, aralkyl, cycloalkoxy, cycloalkylalkoxy, cycloalkylalkanoyl, heteroaryl, cycloalkyl, haloalkylthio, hydroxyhaloalkyl, heteroaralkoxy, heterocycloxy, 25 aralkylaryl, heteroaryloxyalkyl, heteroarylthio, and heteroarylsulfonyl.

In an even more preferred embodiment of compounds of Formula I-C,  $n$  is the integer 1;

$R_{16}$  is hydrido;



$R_1$  is haloalkyl with the proviso that  $R_1$  has a higher Cahn-Ingold-Prelog stereochemical system ranking than both  $R_2$  and  $(CHR_3)_n-N(Ap)Qp$  wherein Ap is Formula (II-P) and Qp is Formula (III-P);



5         $R_2$  is hydrido;

$R_2$  can be selected from the group consisting of alkyl, haloalkyl, aryl, and haloalkoxy with the proviso that  $R_2$  has a lower Cahn-Ingold-Prelog system ranking than both  $R_1$  and  $(CHR_3)_n-N(Ap)Qp$ ;

$R_3$  is selected from the group consisting of hydrido, alkyl, and  
 10        haloalkyl with the provisos that  $(CHR_3)_n-N(Ap)Qp$  has a lower Cahn-Ingold-Prelog stereochemical system ranking than  $R_1$  and a higher Cahn-Ingold-Prelog stereochemical system ranking than  $R_2$ ;

Y is alkylene;  
 Z is covalent single bond;

15         $R_{14}$  is hydrido;

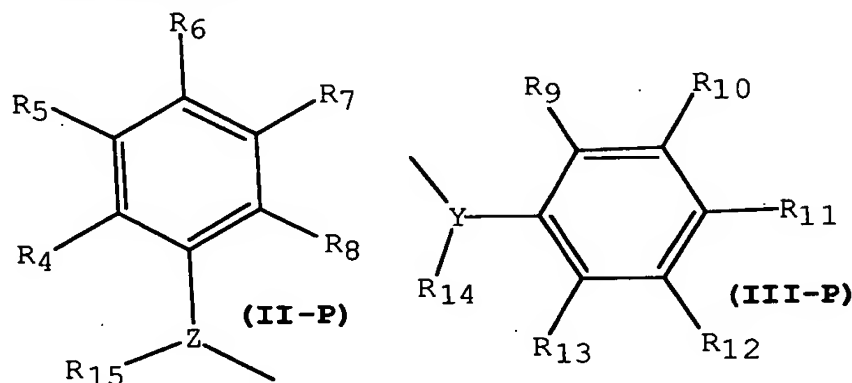
$R_4$ ,  $R_8$ ,  $R_9$ , and  $R_{13}$  are independently selected from the group consisting of hydrido and halo;

$R_5$ ,  $R_6$ ,  $R_7$ ,  $R_{10}$ ,  $R_{11}$ , and  $R_{12}$  are independently selected from the group consisting of hydrido, alkyl, halo, haloalkyl, haloalkoxy, aryl, alkylthio, arylamino, arylthio, aroyl, arylsulfonyl, aryloxy, aralkoxy, heteroaryloxy,  
 20

alkoxy, aralkyl, cycloalkoxy, cycloalkylalkoxy, cycloalkylalkanoyl, heteroaryl, cycloalkyl, haloalkylthio, hydroxyhaloalkyl, heteroaralkoxy, and heteroaryloxyalkyl.

- 5 In an embodiment of compounds of Formula I-C,  
n is an integer selected from 1 to 3;

- $R_1$  is selected from the group consisting of trifluoromethyl, 1,1,2,2-tetrafluoroethoxymethyl, trifluoromethoxymethyl, chloromethyl, fluoromethyl, difluoromethyl, chlorodifluoromethyl, pentafluoroethyl, 2,2,3,3,3-pentafluoropropyl, and heptafluoropropyl with the  
10 proviso that  $R_1$  has a higher Cahn-Ingold-Prelog stereochemical system ranking than both  $R_2$  and  $(CHR_3)_n-N(Ap)Qp$  wherein Ap is Formula (II-P) and Qp is Formula (III-P);



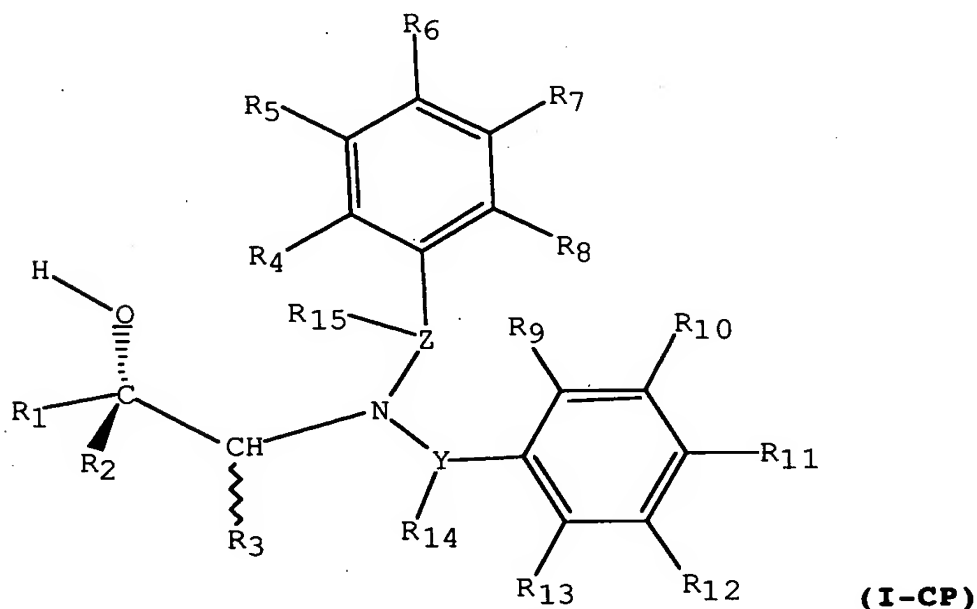
- $R_{16}$  is selected from the group consisting of acetyl, benzoyl, dimethyl  
15 *tert*-butylsilyl, hydrido, and trimethylsilyl;

$R_2$  is hydrido;

- $R_2$  can be selected from the group consisting of methyl, ethyl, propyl, butyl, isopropyl, isobutyl, vinyl, phenyl, 4-trifluoromethylphenyl, 1,1,2,2-tetrafluoroethoxymethyl, chloromethyl, trifluoromethoxymethyl, fluoromethyl, difluoromethyl, 2,2,3,3,3-pentafluoropropyl, and and  
20 pentafluorophenoxymethyl with the proviso that  $R_2$  has a lower Cahn-Ingold-Prelog system ranking than both  $R_1$  and  $(CHR_3)_n-N(Ap)Qp$ ;

- $R_3$  is selected from the group consisting of hydrido, hydroxy, cyano, acetyl, methoxy, ethoxy, methyl, ethyl, propyl, vinyl, phenyl, methoxymethyl, 4-trifluoromethylphenyl, trifluoromethyl, 1,1,2,2-tetrafluoroethoxymethyl, trifluoromethoxymethyl, chloromethyl, fluoromethyl, difluoromethyl, chlorodifluoromethyl, pentafluoroethyl, 2,2,3,3,3-pentafluoropropyl, heptafluoropropyl, pentafluorophenyl, and pentafluorophenoxymethyl with the provisos that  $(CHR_3)_n-N(Ap)Qp$  has a lower Cahn-Ingold-Prelog stereochemical system ranking than  $R_1$  and a higher Cahn-Ingold-Prelog stereochemical system ranking than  $R_2$ .

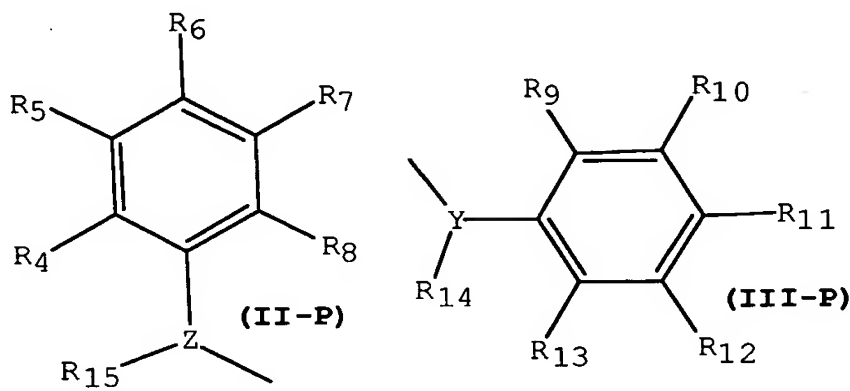
- 10 In a preferred embodiment of compounds of Formula I-C, compounds have the Formula I-CP:



or a pharmaceutically acceptable salt thereof, wherein;

- $R_1$  is selected from the group consisting of trifluoromethyl, 1,1,2,2-tetrafluoroethoxymethyl, trifluoromethoxymethyl, difluoromethyl, chlorodifluoromethyl, and pentafluoroethyl with the proviso that  $R_1$  has a

higher Cahn-Ingold-Prelog stereochemical system ranking than both  $R_2$  and  $(CHR_3)_n-N(Ap)Qp$  wherein Ap is Formula (II-P) and Qp is Formula (III-P);



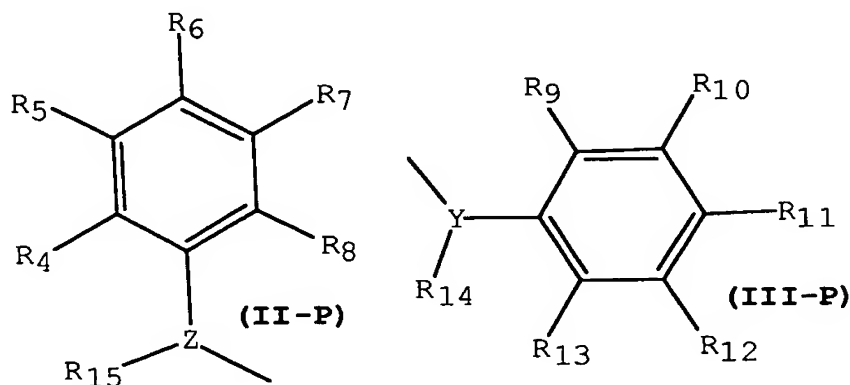
$R_2$  is hydrido;

- 5             $R_2$  can be selected from the group consisting of methyl, ethyl, propyl, butyl, vinyl, phenyl, 4-trifluoromethylphenyl, 1,1,2,2-tetrafluoroethoxymethyl, trifluoromethoxymethyl, difluoromethyl, and 2,2,3,3,3-pentafluoropropyl with the proviso that  $R_2$  has a lower Cahn-Ingold-Prelog system ranking than both  $R_1$  and  $(CHR_3)_n-N(Ap)Qp$ ;
- 10            $R_3$  is selected from the group consisting of hydrido, phenyl, 4-trifluoromethylphenyl, methyl, ethyl, vinyl, methoxymethyl, trifluoromethyl, trifluoromethoxymethyl, difluoromethyl, chlorodifluoromethyl, and pentafluoroethyl with the provisos that  $(CHR_3)_n-N(Ap)Qp$  has a lower Cahn-Ingold-Prelog stereochemical system ranking than  $R_1$  and a higher Cahn-
- 15           Ingold-Prelog stereochemical system ranking than  $R_2$ .

In a even more preferred embodiment of compounds of Formula I-CP,

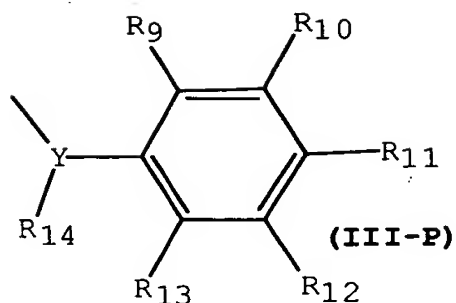
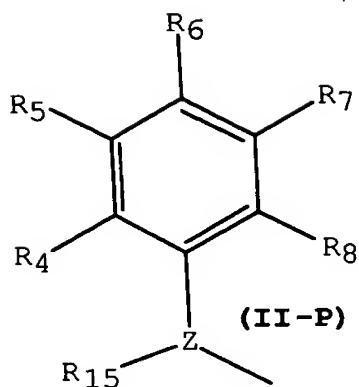
- 20            $R_1$  is selected from the group consisting of trifluoromethyl, 1,1,2,2-tetrafluoroethoxymethyl, trifluoromethoxymethyl, difluoromethyl, chlorodifluoromethyl, and pentafluoroethyl with the proviso that  $R_1$  has a

higher Cahn-Ingold-Prelog stereochemical system ranking than both  $R_2$  and  $(CHR_3)_n-N(Ap)Qp$  wherein Ap is Formula (II-P) and Qp is Formula (III-P);



$R_2$  is hydrido;

- 5             $R_2$  can be selected from the group consisting of methyl, ethyl, phenyl, 4-trifluoromethylphenyl, trifluoromethoxymethyl, 1,1,2,2-tetrafluoroethoxymethyl, difluoromethyl, and 2,2,3,3,3-pentafluoropropyl with the proviso that  $R_2$  has a lower Cahn-Ingold-Prelog system ranking than both  $R_1$  and  $(CHR_3)_n-N(Ap)Qp$ ;
- 10            $R_3$  is selected from the group consisting of hydrido, phenyl, 4-trifluoromethylphenyl, methyl, trifluoromethyl, difluoromethyl, and chlorodifluoromethyl with the provisos that  $(CHR_3)_n-N(Ap)Qp$  has a lower Cahn-Ingold-Prelog stereochemical system ranking than  $R_1$  and a higher Cahn-Ingold-Prelog stereochemical system ranking than  $R_2$ .
- 15           In a most preferred embodiment of compounds of Formula I-CP,  $R_1$  is selected from the group consisting of trifluoromethyl, chlorodifluoromethyl, and pentafluoroethyl with the proviso that  $R_1$  has a higher Cahn-Ingold-Prelog stereochemical system ranking than both  $R_2$  and  $(CHR_3)_n-N(Ap)Qp$  wherein Ap is Formula (II-P) and Qp is Formula (III-P);

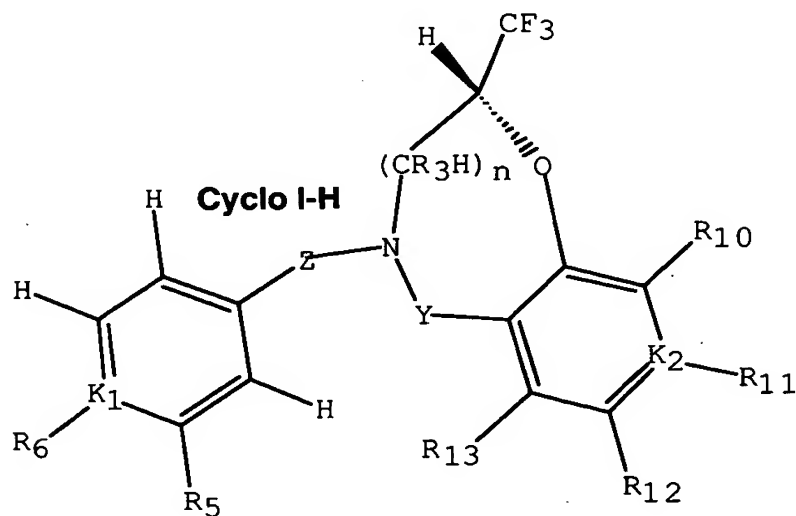


$R_2$  is hydrido;

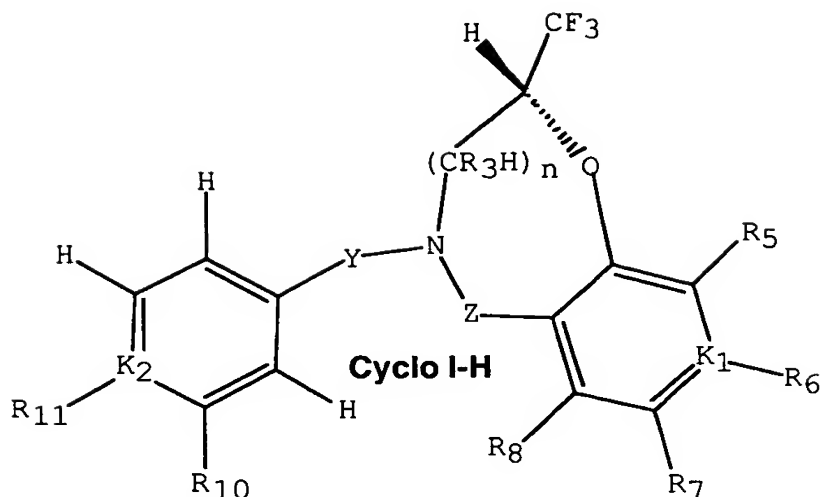
$R_2$  can be phenyl with the proviso that  $R_2$  has a lower Cahn-Ingold-Prelog system ranking than both  $R_1$  and  $(CHR_3)_n-N(Ap)Qp$ ;

- 5  $R_3$  is selected from the group consisting of hydrido, methyl, trifluoromethyl, and difluoromethyl with the provisos that  $(CHR_3)_n-N(Ap)Qp$  has a lower Cahn-Ingold-Prelog stereochemical system ranking than  $R_1$  and a higher Cahn-Ingold-Prelog stereochemical system ranking than  $R_2$ .

10 In another embodiment of compounds of Formulas I-H or I-C, the compounds correspond to the Cyclo I-H Formulas:



and



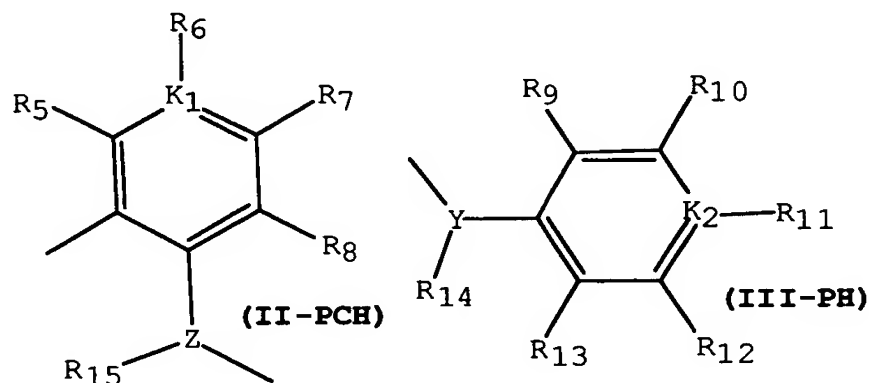
wherein:

$K_1$  and  $K_2$  are independently selected from the group consisting of C and N;

5  $n$  is an integer selected from 1 through 3;

$R_1$  is selected from the group consisting of haloalkyl, haloalkenyl, haloalkoxymethyl, and haloalkenyloxymethyl with the proviso that  $R_1$  has a higher Cahn-Ingold-Prelog stereochemical system ranking than both  $R_2$  and  $(CHR_3)_n-N(Apch)Qph$  wherein Apch is Formula (II-PCH) and Qph is

10 Formula (III-PH);



$R_2$  is hydrido;

- $R_2$  is selected from the group consisting of aryl, aralkyl, alkyl, alkenyl, alkoxyalkyl, alkenyloxyalkyl, haloalkyl, haloalkenyl, halocycloalkyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, dicyanoalkyl, and carboalkoxycyanoalkyl with the proviso that  $R_2$  has a lower Cahn-Ingold-Prelog system ranking than both  $R_1$  and  $(CHR_3)_n-N(Apch)Qph$ ;

- $R_3$  is selected from the group consisting of hydrido, hydroxy, halo, cyano, aryl, aralkyl, acyl, alkoxy, alkyl, alkenyl, alkoxyalkyl, heteroaryl, alkenyloxyalkyl, haloalkyl, haloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, monocyanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, carboxamide, and carboxamidoalkyl with the provisos that  $(CHR_3)_n-N(Apch)Qph$  has a lower Cahn-Ingold-Prelog stereochemical system ranking than  $R_1$  and a higher Cahn-Ingold-Prelog stereochemical system ranking than  $R_2$ ;

- $Y$  is selected from the group consisting of a covalent single bond and  $(C(R_{14})_2)_q$  wherein  $q$  is an integer selected from 1 through 2;

- $R_{14}$  is selected from the group consisting of hydrido, hydroxy, cyano, hydroxyalkyl, acyl, alkoxy, alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkyl, haloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, monocarboalkoxyalkyl, monocyanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, carboalkoxy, carboxamide, and carboxamidoalkyl;

- $Z$  is selected from the group consisting of covalent single bond,  $(C(R_{15})_2)_q$  wherein  $q$  is an integer selected from 1 through 2, and  $(CH(R_{15}))_j-W-(CH(R_{15}))_k$  wherein  $j$  and  $k$  are integers independently selected from 0 through 1;

- $W$  is selected from the group consisting of O, C(O), S, S(O), and S(O)<sub>2</sub>;



$R_{15}$  is selected from the group consisting of hydrido, cyano, hydroxyalkyl, acyl, alkoxy, alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkyl, haloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, monocarboalkoxyalkyl, monocyanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, carboalkoxy, carboxamide, and carboxamidoalkyl;

$R_8$ ,  $R_9$ , and  $R_{13}$  are independently selected from the group consisting of hydrido, halo, haloalkyl, and alkyl ;

$R_5$ ,  $R_6$ ,  $R_7$ ,  $R_{10}$ ,  $R_{11}$ , and  $R_{12}$  are independently selected from the group consisting of hydrido, carboxy, heteroaralkylthio, heteroaralkoxy, cycloalkylamino, acylalkyl, acylalkoxy, aroylalkoxy, heterocyclyloxy, aralkylaryl, aralkyl, aralkenyl, aralkynyl, heterocyclyl, perhaloaralkyl, aralkylsulfonyl, aralkylsulfonylalkyl, aralkylsulfinyl, aralkylsulfinylalkyl, halocycloalkyl, halocycloalkenyl, cycloalkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, heteroaryl amino, N-heteroaryl amino-N-alkyl amino, heteroaryl aminoalkyl, haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxylalkyl, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, cycloalkoxyalkyl, cycloalkylalkoxy, cycloalkenyloxyalkyl, cycloalkylenedioxy, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxy, halocycloalkenyloxyalkyl, hydroxy, amino, thio, nitro, lower alkyl amino, alkylthio, alkylthioalkyl, aryl amino, aralkyl amino, arylthio, arylthioalkyl, heteroaralkoxyalkyl, alkylsulfinyl, alkylsulfinylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, heteroaryl sulfinylalkyl, heteroaryl sulfonylalkyl, alkylsulfonyl, alkylsulfonylalkyl, haloalkylsulfinylalkyl, haloalkylsulfonylalkyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoaryl amidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, heterocyclylsulfonyl, heterocyclylthio, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkenyloxy, alkenyloxyalkyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkylalkanoyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, heteroaralkynyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl,

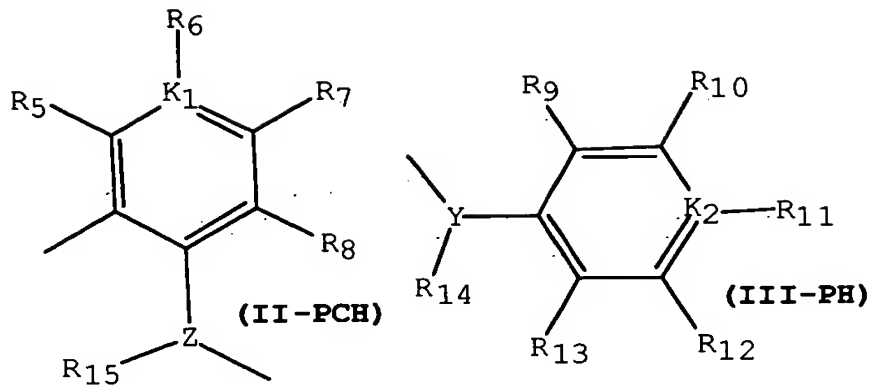
partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, heteroaralkyl, arylalkenyl, heteroarylalkenyl, carboxyalkyl, carboalkoxy, alkoxy-carboxamido, alkylamidocarbonylamido, arylamidocarbonylamido, carboalkoxyalkyl, carboalkoxyalkenyl, carboaralkoxy, carboxamido,  
 5 carboxamidoalkyl, cyano, carbohaloalkoxy, phosphono, phosphonoalkyl, diaralkoxyphosphono, and diaralkoxyphosphonoalkyl;

$R_5$  and  $R_6$ ,  $R_6$  and  $R_7$ ,  $R_7$  and  $R_8$ ,  $R_9$  and  $R_{10}$ ,  $R_{10}$  and  $R_{11}$ ,  $R_{11}$

and  $R_{12}$ , and  $R_{12}$  and  $R_{13}$  can be independently selected to form spacer pairs wherein a spacer pair is taken together to form a linear moiety having from 3  
 10 through 6 contiguous atoms connecting the points of bonding of said spacer pair members to form a ring selected from the group consisting of a cycloalkenyl ring having 5 through 8 contiguous members, a partially saturated heterocyclyl ring having 5 through 8 contiguous members, a heteroaryl ring having 5 through 6 contiguous members, and an aryl with the provisos that no  
 15 more than one of the group consisting of spacer pairs  $R_5$  and  $R_6$ ,  $R_6$  and  $R_7$ , and  $R_7$  and  $R_8$ , can be used at the same time and that no more than one of the group consisting of spacer pairs  $R_9$  and  $R_{10}$ ,  $R_{10}$  and  $R_{11}$ ,  $R_{11}$  and  $R_{12}$ , and  $R_{12}$  and  $R_{13}$  can be used at the same time.

20 In an embodiment of compounds of Formula Cyclo I-H,  
 $n$  is the integer 1;

$R_1$  is selected from the group consisting of trifluoromethyl, 1,1,2,2-tetrafluoroethoxymethyl, trifluoromethoxymethyl, difluoromethyl, chlorodifluoromethyl, and pentafluoroethyl with the proviso that  $R_1$  has a  
 25 higher Cahn-Ingold-Prelog stereochemical system ranking than both  $R_2$  and  $(CHR_3)_n$ -N(Apch)Qph wherein Apch is Formula (II-PCH) and Qph is Formula (III-PH);



$R_2$  is hydrido;

$R_2$  is selected from the group consisting of phenyl,

- 4-trifluoromethylphenyl, vinyl, 1,1,2,2-tetrafluoroethoxymethyl,  
 5 trifluoromethoxymethyl, difluoromethyl, and 2,2,3,3,3-pentafluoropropyl with  
 the proviso that  $R_2$  has a lower Cahn-Ingold-Prelog system ranking than both  
 $R_1$  and  $(CHR_3)_n-N(Apch)Qph$ ;

- $R_3$  is selected from the group consisting of hydrido, methyl, ethyl,  
 vinyl, phenyl, 4-trifluoromethylphenyl, methoxymethyl, trifluoromethyl;  
 10 trifluoromethoxymethyl, difluoromethyl, chlorodifluoromethyl, and  
 pentafluoroethyl with the provisos that  $(CHR_3)_n-N(Apch)Qph$  has a lower  
 Cahn-Ingold-Prelog stereochemical system ranking than  $R_1$  and a higher Cahn-  
 Ingold-Prelog stereochemical system ranking than  $R_2$ .

- 15 In another embodiment of compounds of Formula Cyclo I-H,  
 $n$  is the integer 1;

$R_1$  is selected from the group consisting of trifluoromethyl, 1,1,2,2-  
 tetrafluoroethoxymethyl, trifluoromethoxymethyl, difluoromethyl,  
 chlorodifluoromethyl, and pentafluoroethyl;

- 20  $R_2$  is hydrido;

$R_3$  is selected from the group consisting of hydrido, methyl, ethyl, vinyl, phenyl, 4-trifluoromethylphenyl, methoxymethyl, trifluoromethyl, trifluoromethoxymethyl, difluoromethyl, chlorodifluoromethyl, and pentafluoroethyl with the provisos that  $(CHR_3)_n-N(Apch)Qph$  has a lower

- 5 Cahn-Ingold-Prelog stereochemical system ranking than  $R_1$  and a higher Cahn-Ingold-Prelog stereochemical system ranking than  $R_2$ .

In a preferred embodiment of compounds of Formulas I-H, I-C, I-CP, and Cyclo I-H,

- 10 Y is selected from the group consisting of methylene, ethylene, and ethylidene;

Z is covalent single bond;

$R_4$ ,  $R_8$ ,  $R_9$ , and  $R_{13}$  are independently selected from the group consisting of hydrido and fluoro with the proviso that there is no  $R_4$ ,  $R_8$ ,  $R_9$ , or  $R_{13}$  when the embodiment is a compound of Formula Cyclo I-H;

- 15  $R_5$  and  $R_{10}$  are independently selected from the group consisting of 4-aminophenoxy, benzoyl, benzyl, benzyloxy, 5-bromo-2-fluorophenoxy, 4-bromo-3-fluorophenoxy, 4-bromo-2-nitrophenoxy, 3-bromobenzyloxy, 4-bromobenzyloxy, 4-bromophenoxy, 5-bromopyrid-2-yloxy, 4-butoxyphenoxy, chloro, 3-chlorobenzyl, 2-chlorophenoxy,
- 20 4-chlorophenoxy, 4-chloro-3-ethylphenoxy, 3-chloro-4-fluorobenzyl, 3-chloro-4-fluorophenyl, 3-chloro-2-fluorobenzyloxy, 3-chlorobenzyloxy, 4-chlorobenzyloxy, 4-chloro-3-methylphenoxy, 2-chloro-4-fluorophenoxy, 4-chloro-2-fluorophenoxy, 4-chlorophenoxy, 3-chloro-4-ethylphenoxy, 3-chloro-4-methylphenoxy, 3-chloro-4-fluorophenoxy,
- 25 4-chloro-3-fluorophenoxy, 4-chlorophenylamino, 5-chloropyrid-3-yloxy, 2-cyanopyrid-3-yloxy, 4-cyanophenoxy, cyclobutoxy, cyclobutyl, cyclohexoxy, cyclohexylmethoxy, cyclopentoxy, cyclopentyl, cyclopentylcarbonyl, cyclopropyl, cyclopropylmethoxy, cyclopropoxy, 2,3-dichlorophenoxy, 2,4-dichlorophenoxy, 2,4-dichlorophenyl,
- 30 3,5-dichlorophenyl, 3,5-dichlorobenzyl, 3,4-dichlorophenoxy,

- 3,4-difluorophenoxy, 2,3-difluorobenzoyloxy, 2,4-difluorobenzoyloxy,  
 3,4-difluorobenzoyloxy, 2,5-difluorobenzoyloxy, 3,5-difluorophenoxy,  
 3,4-difluorophenyl, 3,5-difluorobenzoyloxy, 4-difluoromethoxybenzoyloxy,  
 2,3-difluorophenoxy, 2,4-difluorophenoxy, 2,5-difluorophenoxy,  
 5 3,5-dimethoxyphenoxy, 3-dimethylaminophenoxy, 3,5-dimethylphenoxy,  
 3,4-dimethylphenoxy, 3,4-dimethylbenzyl, 3,4-dimethylbenzoyloxy,  
 3,5-dimethylbenzoyloxy, 2,2-dimethylpropoxy, 1,3-dioxan-2-yl,  
 1,4-dioxan-2-yl, 1,3-dioxolan-2-yl, ethoxy, 4-ethoxyphenoxy,  
 4-ethylbenzoyloxy, 3-ethylphenoxy, 4-ethylaminophenoxy,  
 10 3-ethyl-5-methylphenoxy, fluoro, 4-fluoro-3-methylbenzyl,  
 4-fluoro-3-methylphenyl, 4-fluoro-3-methylbenzoyl, 4-fluorobenzoyloxy,  
 2-fluoro-3-methylphenoxy, 3-fluoro-4-methylphenoxy, 3-fluorophenoxy,  
 3-fluoro-2-nitrophenoxy, 2-fluoro-3-trifluoromethylbenzoyloxy,  
 3-fluoro-5-trifluoromethylbenzoyloxy, 4-fluoro-2-trifluoromethylbenzoyloxy,  
 15 4-fluoro-3-trifluoromethylbenzoyloxy, 2-fluorophenoxy, 4-fluorophenoxy,  
 2-fluoro-3-trifluoromethylphenoxy, 2-fluorobenzoyloxy,  
 4-fluorophenylamino, 2-fluoro-4-trifluoromethylphenoxy,  
 4-fluoropyrid-2-yloxy, 2-furyl, 3-furyl, heptafluoropropyl,  
 1,1,1,3,3,3-hexafluoropropyl, 2-hydroxy-3,3,3-trifluoropropoxy,  
 20 3-iodobenzoyloxy, isobutyl, isobutylamino, isobutoxy, 3-isoxazolyl,  
 4-isoxazolyl, 5-isoxazolyl, isopropoxy, isopropyl, 4-isopropylbenzoyloxy,  
 3-isopropylphenoxy, 4-isopropylphenoxy, isopropylthio,  
 4-isopropyl-3-methylphenoxy, 3-isothiazolyl, 4-isothiazolyl,  
 5-isothiazolyl, 3-methoxybenzyl, 4-methoxycarbonylbutoxy,  
 25 3-methoxycarbonylprop-2-enyloxy, 4-methoxyphenyl,  
 3-methoxyphenylamino, 4-methoxyphenylamino, 3-methylbenzoyloxy,  
 4-methylbenzoyloxy, 3-methylphenoxy, 3-methyl-4-methylthiophenoxy,  
 4-methylphenoxy, 1-methylpropoxy, 2-methylpyrid-5-yloxy,  
 4-methylthiophenoxy, 2-naphthylloxy, 2-nitrophenoxy, 4-nitrophenoxy,  
 30 3-nitrophenyl, 4-nitrophenylthio, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl,  
 pentafluoroethyl, pentafluoroethylthio, 2,2,3,3,3-pentafluoropropyl,  
 1,1,3,3,3-pentafluoropropyl, 1,1,2,2,3-pentafluoropropyl, phenoxy,  
 phenylamino, 1-phenylethoxy, phenylsulfonyl, 4-propanoylphenoxy,  
 propoxy, 4-propylphenoxy, 4-propoxyphenoxy, thiophen-3-yl, *sec*-butyl,  
 35 4-*sec*-butylphenoxy, *tert*-butoxy, 3-*tert*-butylphenoxy, 4-*tert*-butylphenoxy,  
 1,1,2,2-tetrafluoroethoxy, tetrahydrofuran-2-yl,

- 2-(5,6,7,8-tetrahydronaphthyl), thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, thiophen-2-yl, 2,3,5-trifluorobenzyloxy, 2,2,2-trifluoroethoxy, 2,2,2-trifluoroethyl, 3,3,3-trifluoro-2-hydroxypropyl, trifluoromethoxy, 3-trifluoromethoxybenzyloxy, 4-trifluoromethoxybenzyloxy,
- 5 3-trifluoromethoxyphenoxy, 4-trifluoromethoxyphenoxy, trifluoromethyl, 3-trifluoromethylbenzyloxy, 4-trifluoromethylbenzyloxy, 2,4-bis-trifluoromethylbenzyloxy, 1,1-bis-trifluoromethyl-1-hydroxymethyl, 3-trifluoromethylbenzyl, 3,5-bis-trifluoromethylbenzyloxy, 4-trifluoromethylphenoxy, 3-trifluoromethylphenoxy,
- 10 3-trifluoromethylphenyl, 3-trifluoromethylthiobenzyloxy, 4-trifluoromethylthiobenzyloxy, 2,3,4-trifluorophenoxy, 2,3,4-trifluorophenyl, 2,3,5-trifluorophenoxy, 3,4,5-trimethylphenoxy, 3-difluoromethoxyphenoxy, 3-pentafluoroethylphenoxy, 3-(1,1,2,2-tetrafluoroethoxy)phenoxy, 3-trifluoromethylthiophenoxy, and
- 15 trifluoromethylthio;

$R_6$  and  $R_{11}$  are independently selected from the group consisting of chloro, fluoro, hydrido, pentafluoroethyl, 1,1,2,2-tetrafluoroethoxy, trifluoromethyl, and trifluoromethoxy;

- $R_7$  and  $R_{12}$  are independently selected from the group consisting of
- 20 hydrido, fluoro, and trifluoromethyl.

In an even more preferred embodiment of compounds of Formulas I-H, I-C, I-CP, and Cyclo I-H,

- Y is methylene;
- 25 Z is covalent single bond;

$R_4$ ,  $R_8$ ,  $R_9$ , and  $R_{13}$  are independently selected from the group consisting of hydrido and fluoro with the proviso that there is no  $R_4$ ,  $R_8$ ,  $R_9$ , or  $R_{13}$  when the embodiment is a compound of Formula Cyclo I-H;

- $R_5$  and  $R_{10}$  are independently selected from the group consisting of
- 30 benzyloxy, 5-bromo-2-fluorophenoxy, 4-bromo-3-fluorophenoxy, 3-bromobenzyloxy, 4-bromophenoxy, 4-butoxyphenoxy, 3-chlorobenzyloxy, 2-chlorophenoxy, 4-chloro-3-ethylphenoxy,

- 4-chloro-3-methylphenoxy, 2-chloro-4-fluorophenoxy,  
 4-chloro-2-fluorophenoxy, 4-chlorophenoxy, 3-chloro-4-ethylphenoxy,  
 3-chloro-4-methylphenoxy, 3-chloro-4-fluorophenoxy,  
 4-chloro-3-fluorophenoxy, 4-chlorophenylamino, 5-chloropyrid-3-yloxy,  
 5 cyclobutoxy, cyclobutyl, cyclohexylmethoxy, cyclopentoxo, cyclopentyl,  
 cyclopentylcarbonyl, cyclopropylmethoxy, 2,3-dichlorophenoxy,  
 2,4-dichlorophenoxy, 2,4-dichlorophenyl, 3,5-dichlorophenyl,  
 3,5-dichlorobenzyl, 3,4-dichlorophenoxy, 3,4-difluorophenoxy,  
 2,3-difluorobenzoyloxy, 3,5-difluorobenzoyloxy, difluoromethoxy,  
 10 3,5-difluorophenoxy, 3,4-difluorophenyl, 2,3-difluorophenoxy,  
 2,4-difluorophenoxy, 2,5-difluorophenoxy, 3,5-dimethoxyphenoxy,  
 3-dimethylaminophenoxy, 3,4-dimethylbenzoyloxy, 3,5-dimethylbenzoyloxy,  
 3,5-dimethylphenoxy, 3,4-dimethylphenoxy, 1,3-dioxolan-2-yl,  
 3-ethylbenzoyloxy, 3-ethylphenoxy, 4-ethylaminophenoxy,  
 15 3-ethyl-5-methylphenoxy, 4-fluoro-3-methylbenzyl, 4-fluorobenzoyloxy,  
 2-fluoro-3-methylphenoxy, 3-fluoro-4-methylphenoxy, 3-fluorophenoxy,  
 3-fluoro-2-nitrophenoxy, 2-fluoro-3-trifluoromethylbenzoyloxy,  
 3-fluoro-5-trifluoromethylbenzoyloxy, 2-fluorophenoxy, 4-fluorophenoxy,  
 2-fluoro-3-trifluoromethylphenoxy, 2-fluorobenzoyloxy,  
 20 4-fluorophenylamino, 2-fluoro-4-trifluoromethylphenoxy, 2-furyl, 3-furyl,  
 heptafluoropropyl, 1,1,1,3,3,3-hexafluoropropyl,  
 2-hydroxy-3,3,3-trifluoropropoxy, isobutoxy, isobutyl, 3-isoxazolyl,  
 4-isoxazolyl, 5-isoxazolyl, isopropoxy,  
 3-isopropylbenzoyloxy, 3-isopropylphenoxy, isopropylthio,  
 25 4-isopropyl-3-methylphenoxy, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl,  
 3-methoxybenzyl, 4-methoxyphenylamino, 3-methylbenzoyloxy,  
 4-methylbenzoyloxy, 3-methylphenoxy, 3-methyl-4-methylthiophenoxy,  
 4-methylphenoxy, 1-methylpropoxy, 2-methylpyrid-5-yloxy,  
 4-methylthiophenoxy, 2-naphthyl, 2-nitrophenoxy, 4-nitrophenoxy,  
 30 3-nitrophenyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, pentafluoroethyl,  
 pentafluoroethylthio, 2,2,3,3,3-pentafluoropropyl,  
 1,1,3,3,3-pentafluoropropyl, 1,1,2,2,3-pentafluoropropyl, phenoxy,  
 phenylamino, 1-phenylethoxy, 4-propylphenoxy, 4-propoxyphenoxy,  
 thiophen-3-yl, tert -butoxy, 3-tert -butylphenoxy, 4-tert -butylphenoxy,  
 35 1,1,2,2-tetrafluoroethoxy, tetrahydrofuran-2-yl,  
 2-(5,6,7,8-tetrahydronaphthyl), thiazol-2-yl, thiazol-4-yl, thiazol-5-yl,  
 thiophen-2-yl, 2,2,2-trifluoroethoxy, 2,2,2-trifluoroethyl,

- 3,3,3-trifluoro-2-hydroxypropyl, trifluoromethoxy,  
 3-trifluoromethoxybenzyloxy, 4-trifluoromethoxybenzyloxy,  
 4-trifluoromethoxyphenoxy, 3-trifluoromethoxyphenoxy, trifluoromethyl,  
 3-trifluoromethylbenzyloxy, 1,1-bis-trifluoromethyl-1-hydroxymethyl,  
 5 3-trifluoromethylbenzyl, 3,5-bis-trifluoromethylbenzyloxy,  
 4-trifluoromethylphenoxy, 3-trifluoromethylphenoxy,  
 3-trifluoromethylphenyl, 2,3,4-trifluorophenoxy, 2,3,5-trifluorophenoxy,  
 3,4,5-trimethylphenoxy, 3-difluoromethoxyphenoxy,  
 3-pentafluoroethylphenoxy, 3-(1,1,2,2-tetrafluoroethoxy)phenoxy,  
 10 3-trifluoromethylthiophenoxy, 3-trifluoromethylthiobenzyloxy, and  
 trifluoromethylthio;

$R_6$  and  $R_{11}$  are independently selected from the group consisting of  
 chloro, fluoro, hydrido, pentafluoroethyl, 1,1,2,2-tetrafluoroethoxy, and  
 trifluoromethyl;

- 15  $R_7$  and  $R_{12}$  are independently selected from the group consisting of  
 hydrido, fluoro, and trifluoromethyl.

In a most preferred embodiment of compounds of Formulas I-H, I-C,  
 I-CP, and Cyclo I-H,

- 20 Y is methylene;  
 Z is covalent single bond;

$R_4$ ,  $R_8$ ,  $R_9$ , and  $R_{13}$  are independently selected from the group  
 consisting of hydrido and fluoro with the proviso that there is no  $R_4$ ,  $R_8$ ,  $R_9$ ,  
 or  $R_{13}$  when the embodiment is a compound of Formula Cyclo I-H;

- 25  $R_5$  is selected from the group consisting of 5-bromo-2-fluorophenoxy,  
 4-chloro-3-ethylphenoxy, 2,3-dichlorophenoxy, 3,4-dichlorophenoxy, 3-  
 difluoromethoxyphenoxy, 3,5-dimethylphenoxy, 3,4-dimethylphenoxy, 3-  
 ethylphenoxy, 3-ethyl-5-methylphenoxy,  
 4-fluoro-3-methylphenoxy, 4-fluorophenoxy, 3-isopropylphenoxy,  
 30 3-methylphenoxy, 3-pentafluoroethylphenoxy, 3-tert-butylphenoxy,  
 3-(1,1,2,2-tetrafluoroethoxy)phenoxy, 2-(5,6,7,8-tetrahydronaphthyl)oxy,  
 3-trifluoromethoxybenzyloxy, 3-trifluoromethoxyphenoxy,



3-trifluoromethylbenzyloxy, and 3-trifluoromethylthiophenoxy;

$R_{10}$  is selected from the group consisting of cyclopentyl, 1,1,2,2-tetrafluoroethoxy, 2-furyl, 1,1-bis-trifluoromethyl-1-hydroxymethyl, isobutyl, isopropoxy, pentafluoroethyl, trifluoromethoxy, trifluoromethyl, and  
5 trifluoromethylthio;

$R_6$  and  $R_{11}$  are independently selected from the group consisting of fluoro and hydrido;

$R_7$  and  $R_{12}$  are independently selected from the group consisting of  
10 hydrido and fluoro.

## DEFINITIONS

The use of generic terms in the description of the compounds are herein defined for clarity.

15 Standard single letter elemental symbols are used to represent specific types of atoms unless otherwise defined. The symbol "C" represents a carbon atom. The symbol "O" represents an oxygen atom. The symbol "N" represents a nitrogen atom. The symbol "P" represents a phosphorus atom. The symbol "S" represents a sulfur atom. The symbol "H" represents a hydrogen atom. Double  
20 letter elemental symbols are used as defined for the elements of the periodical table (i.e., Cl represents chlorine, Se represents selenium, etc.).

As utilized herein, the term "alkyl", either alone or within other terms such as "haloalkyl" and "alkylthio", means an acyclic alkyl radical containing from 1 to about 10, preferably from 1 to about 8 carbon atoms and more preferably 1 to  
25 about 6 carbon atoms. Said alkyl radicals may be optionally substituted with groups as defined below. Examples of such radicals include methyl, ethyl, chloroethyl, hydroxyethyl, n-propyl, oxopropyl, isopropyl, n-butyl, cyanobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, aminopentyl, iso-amyl, hexyl, octyl and the like.

30

The term "alkenyl" refers to an unsaturated, acyclic hydrocarbon radical in so much as it contains at least one double bond. Such alkenyl radicals contain from about 2 to about 10 carbon atoms, preferably from about 2 to about 8 carbon atoms and more preferably 2 to about 6 carbon atoms. Said alkenyl radicals may be optionally substituted with groups as defined below. Examples of suitable alkenyl radicals include propenyl, 2-chloropropenyl, buten-1-yl, isobutenyl, penten-1-yl, 2-2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, 3-hydroxyhexen-1-yl, hepten-1-yl, and octen-1-yl, and the like.

The term "alkynyl" refers to an unsaturated, acyclic hydrocarbon radical in so much as it contains one or more triple bonds, such radicals containing about 2 to about 10 carbon atoms, preferably having from about 2 to about 8 carbon atoms and more preferably having 2 to about 6 carbon atoms. Said alkynyl radicals may be optionally substituted with groups as defined below. Examples of suitable alkynyl radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyn-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals and the like.

The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a "hydroxyl" radical, one hydrido radical may be attached to a carbon atom to form a "methine" radical ( $=\text{CH}-$ ), or two hydrido radicals may be attached to a carbon atom to form a "methylene" ( $-\text{CH}_2-$ ) radical.

The term "carbon" radical denotes a carbon atom without any covalent bonds and capable of forming four covalent bonds.

The term "cyano" radical denotes a carbon radical having three of four covalent bonds shared by a nitrogen atom.

The term "hydroxyalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with a hydroxyl as defined above. Specifically embraced are monohydroxyalkyl, dihydroxyalkyl and polyhydroxyalkyl radicals.

The term "alkanoyl" embraces radicals wherein one or more of the terminal alkyl carbon atoms are substituted with one or more carbonyl radicals as defined below. Specifically embraced are monocarbonylalkyl and dicarbonylalkyl radicals. Examples of monocarbonylalkyl radicals include formyl, acetyl, and pentanoyl. Examples of dicarbonylalkyl radicals include oxalyl, malonyl, and succinyl.

The term "alkylene" radical denotes linear or branched radicals having from 1 to about 10 carbon atoms and having attachment points for two or more covalent bonds. Examples of such radicals are methylene, ethylene, ethylidene, methylethylene, and isopropylidene.

- 5       The term "alkenylene" radical denotes linear or branched radicals having from 2 to about 10 carbon atoms, at least one double bond, and having attachment points for two or more covalent bonds. Examples of such radicals are 1,1-vinylidene ( $\text{CH}_2=\text{C}$ ), 1,2-vinylidene ( $-\text{CH}=\text{CH}-$ ), and 1,4-butadienyl ( $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ ).

- 10       The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms.

- 15       The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either a bromo, chloro or a fluoro atom within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. More preferred haloalkyl radicals are "lower haloalkyl" radicals having one to about six carbon atoms. Examples of such haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trifluoroethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl.

- 25       The term "hydroxyhaloalkyl" embraces radicals wherein any one or more of the haloalkyl carbon atoms is substituted with hydroxy as defined above. Examples of "hydroxyhaloalkyl" radicals include hexafluorohydroxypropyl.

- 30       The term "haloalkylene radical" denotes alkylene radicals wherein any one or more of the alkylene carbon atoms is substituted with halo as defined above. Dihalo alkylene radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkylene radicals may have more than two of the same halo atoms or a combination of different halo radicals. More preferred haloalkylene radicals are "lower haloalkylene" radicals having one to about six carbon atoms. Examples of "haloalkylene" radicals include difluoromethylene, tetrafluoroethylene, tetrachloroethylene,
- 35

alkyl substituted monofluoromethylene, and aryl substituted trifluoromethylene.

5 The term "haloalkenyl" denotes linear or branched radicals having from 1 to about 10 carbon atoms and having one or more double bonds wherein any one or more of the alkenyl carbon atoms is substituted with halo as defined above. Dihaloalkenyl radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkenyl radicals may have more than two of the same halo atoms or a combination of different halo radicals.

10 The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. More preferred alkoxy  
15 radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy, isopropoxy and *tert*-butoxy alkyls. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" and "haloalkoxyalkyl" radicals. Examples of such haloalkoxy radicals include  
20 fluoromethoxy, chloromethoxy, trifluoromethoxy, difluoromethoxy, trifluoroethoxy, fluoroethoxy, tetrafluoroethoxy, pentafluoroethoxy, and fluoropropoxy. Examples of such haloalkoxyalkyl radicals include fluoromethoxymethyl, chloromethoxyethyl, trifluoromethoxymethyl, difluoromethoxyethyl, and trifluoroethoxymethyl.

25 The terms "alkenyloxy" and "alkenyloxyalkyl" embrace linear or branched oxy-containing radicals each having alkenyl portions of two to about ten carbon atoms, such as ethenyloxy or propenyloxy radical. The term "alkenyloxyalkyl" also embraces alkenyl radicals having one or more alkenyloxy radicals attached to the alkyl radical, that is, to form  
30 monoalkenyloxyalkyl and dialkenyloxyalkyl radicals. More preferred alkenyloxy radicals are "lower alkenyloxy" radicals having two to six carbon atoms. Examples of such radicals include ethenyloxy, propenyloxy, butenyloxy, and isopropenyloxy alkyls. The "alkenyloxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or  
35 bromo, to provide "haloalkenyloxy" radicals. Examples of such radicals include trifluoroethenyloxy, fluoroethenyloxy, difluoroethenyloxy, and fluoropropenyloxy.

The term "haloalkoxyalkyl" also embraces alkyl radicals having one or more haloalkoxy radicals attached to the alkyl radical, that is, to form monohaloalkoxyalkyl and dihaloalkoxyalkyl radicals. The term "haloalkenyloxy" also embraces oxygen radicals having one or more haloalkenyloxy radicals attached to the oxygen radical, that is, to form monohaloalkenyloxy and dihaloalkenyloxy radicals. The term "haloalkenyloxyalkyl" also embraces alkyl radicals having one or more haloalkenyloxy radicals attached to the alkyl radical, that is, to form monohaloalkenyloxyalkyl and dihaloalkenyloxyalkyl radicals.

10 The term "alkylenedioxy" radicals denotes alkylene radicals having at least two oxygens bonded to a single alkylene group. Examples of "alkylenedioxy" radicals include methylenedioxy, ethylenedioxy, alkylsubstituted methylenedioxy, and arylsubstituted methylenedioxy. The term "haloalkylenedioxy" radicals denotes haloalkylene radicals having at least two  
15 oxy groups bonded to a single haloalkyl group. Examples of "haloalkylenedioxy" radicals include difluoromethylenedioxy, tetrafluoroethylenedioxy, tetrachloroethylenedioxy, alkylsubstituted monofluoromethylenedioxy, and arylsubstituted monofluoromethylenedioxy.

The term "aryl", alone or in combination, means a carbocyclic aromatic  
20 system containing one, two or three rings wherein such rings may be attached together in a pendant manner or may be fused. The term "fused" means that a second ring is present (ie, attached or formed) by having two adjacent atoms in common (ie, shared) with the first ring. The term "fused" is equivalent to the term "condensed". The term "aryl" embraces aromatic radicals such as phenyl,  
25 naphthyl, tetrahydronaphthyl, indane and biphenyl.

The term "perhaloaryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl wherein the aryl radical is substituted with 3 or more halo radicals as defined below.

The term "heterocyclyl" embraces saturated, partially saturated and  
30 unsaturated heteroatom-containing ring-shaped radicals having from 5 through 15 ring members selected from carbon, nitrogen, sulfur and oxygen, wherein at least one ring atom is a heteroatom. Heterocyclyl radicals may contain one, two or three rings wherein such rings may be attached in a pendant manner or may be fused. Examples of saturated heterocyclic radicals include saturated 3  
35 to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms[e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3

nitrogen atoms [e.g. morpholinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl, etc.]. Examples of partially saturated heterocycl

radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals, include unsaturated 5 to 6 membered heteromonocycl

group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.] tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.;

unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indoliziny, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl, etc.], etc.; unsaturated 3 to 6-membered heteromonocyclic

group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.] etc.; unsaturated condensed heterocyclic

group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl, etc.]; unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.] etc.; unsaturated condensed heterocyclic

group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.] and the like. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like.

Said "heterocyclyl" group may have 1 to 3 substituents as defined below. Preferred heterocyclic radicals include five to twelve membered fused or unfused radicals. Non-limiting examples of heterocyclic radicals include pyrrolyl, pyridinyl, pyridyloxy, pyrazolyl, triazolyl, pyrimidinyl, pyridazinyl, oxazolyl, thiazolyl, imidazolyl, indolyl, thiophenyl, furanyl, tetrazolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolindinyl, 1,3-dioxolanyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, 2H-pyranyl, 4H-pyranyl,

piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, benzo(b)thiophenyl, benzimidazolyl, quinolinyl, tetraazolyl, and the like.

The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals  $\text{-SO}_2\text{-}$ . "Alkylsulfonyl", embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. "Alkylsulfonylalkyl", embraces alkylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above. "Haloalkylsulfonyl", embraces haloalkyl radicals attached to a sulfonyl radical, where haloalkyl is defined as above. "Haloalkylsulfonylalkyl", embraces haloalkylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above. The term "aminosulfonyl" denotes an amino radical attached to a sulfonyl radical.

The term "sulfinyl", whether used alone or linked to other terms such as alkylsulfinyl, denotes respectively divalent radicals  $\text{-S(O)-}$ . "Alkylsulfinyl", embraces alkyl radicals attached to a sulfinyl radical, where alkyl is defined as above. "Alkylsulfinylalkyl", embraces alkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above. "Haloalkylsulfinyl", embraces haloalkyl radicals attached to a sulfinyl radical, where haloalkyl is defined as above. "Haloalkylsulfinylalkyl", embraces haloalkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Examples of such radicals include benzyl, diphenylmethyl, triphenylmethyl, phenylethyl and diphenylethyl. The terms benzyl and phenylmethyl are interchangeable.

The term "heteroaralkyl" embraces heteroaryl-substituted alkyl radicals wherein the heteroaralkyl radical may be additionally substituted with three or more substituents as defined above for aralkyl radicals. The term "perhaloaralkyl" embraces aryl-substituted alkyl radicals wherein the aralkyl radical is substituted with three or more halo radicals as defined above.

The term "aralkylsulfinyl", embraces aralkyl radicals attached to a sulfinyl radical, where aralkyl is defined as above. "Aralkylsulfinylalkyl", embraces aralkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "aralkylsulfonyl", embraces aralkyl radicals attached to a sulfonyl radical, where aralkyl is defined as above. "Aralkylsulfonylalkyl",

embraces aralkylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "cycloalkyl" embraces radicals having three to ten carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to seven carbon atoms. Examples include radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The term "cycloalkylalkyl" embraces cycloalkyl-substituted alkyl radicals. Preferable cycloalkylalkyl radicals are "lower cycloalkylalkyl" radicals having cycloalkyl radicals attached to alkyl radicals having one to six carbon atoms. Examples of such radicals include cyclohexylhexyl. The term "cycloalkenyl" embraces radicals having three to ten carbon atoms and one or more carbon-carbon double bonds. Preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having three to seven carbon atoms. Examples include radicals such as cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl. The term "halocycloalkyl" embraces radicals wherein any one or more of the cycloalkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohalocycloalkyl, dihalocycloalkyl and polyhalocycloalkyl radicals. A monohalocycloalkyl radical, for one example, may have either a bromo, chloro or a fluoro atom within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhalocycloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. More preferred halocycloalkyl radicals are "lower halocycloalkyl" radicals having three to about eight carbon atoms. Examples of such halocycloalkyl radicals include fluorocyclopropyl, difluorocyclobutyl, trifluorocyclopentyl, tetrafluorocyclohexyl, and dichlorocyclopropyl. The term "halocycloalkenyl" embraces radicals wherein any one or more of the cycloalkenyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohalocycloalkenyl, dihalocycloalkenyl and polyhalocycloalkenyl radicals.

The term "cycloalkoxy" embraces cycloalkyl radicals attached to an oxy radical. Examples of such radicals includes cyclohexoxy and cyclopentoxy. The term "cycloalkoxyalkyl" also embraces alkyl radicals having one or more cycloalkoxy radicals attached to the alkyl radical, that is, to form monocycloalkoxyalkyl and dicycloalkoxyalkyl radicals. Examples of such radicals include cyclohexoxyethyl. The "cycloalkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "halocycloalkoxy" and "halocycloalkoxyalkyl" radicals.



The term "cycloalkylalkoxy" embraces cycloalkyl radicals attached to an alkoxy radical. Examples of such radicals includes cyclohexylmethoxy and cyclopentylmethoxy.

5 The term "cycloalkenyloxy" embraces cycloalkenyl radicals attached to an oxy radical. Examples of such radicals includes cyclohexenyloxy and cyclopentenyloxy. The term "cycloalkenyloxyalkyl" also embraces alkyl radicals having one or more cycloalkenyloxy radicals attached to the alkyl radical, that is, to form monocycloalkenyloxyalkyl and dicycloalkenyloxyalkyl radicals. Examples of such radicals include cyclohexenyloxyethyl. The  
10 "cycloalkenyloxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "halocycloalkenyloxy" and "halocycloalkenyloxyalkyl" radicals.

The term "cycloalkylenedioxy" radicals denotes cycloalkylene radicals having at least two oxygens bonded to a single cycloalkylene group. Examples  
15 of "alkylenedioxy" radicals include 1,2-dioxycyclohexylene.

The term "cycloalkylsulfinyl", embraces cycloalkyl radicals attached to a sulfinyl radical, where cycloalkyl is defined as above. "Cycloalkylsulfinylalkyl", embraces cycloalkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above. The term "Cycloalkylsulfonyl",  
20 embraces cycloalkyl radicals attached to a sulfonyl radical, where cycloalkyl is defined as above. "Cycloalkylsulfonylalkyl", embraces cycloalkylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "cycloalkylalkanoyl" embraces radicals wherein one or more of the cycloalkyl carbon atoms are substituted with one or more carbonyl  
25 radicals as defined below. Specifically embraced are monocarbonylcycloalkyl and dicarbonylcycloalkyl radicals. Examples of monocarbonylcycloalkyl radicals include cyclohexylcarbonyl, cyclohexylacetyl, and cyclopentylcarbonyl. Examples of dicarbonylcycloalkyl radicals include 1,2-dicarbonylcyclohexane..

30 The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having one to six carbon atoms. An example of "lower alkylthio" is methylthio ( $\text{CH}_3\text{-S-}$ ). The "alkylthio" radicals may be further substituted with one or more halo  
35 atoms, such as fluoro, chloro or bromo, to provide "haloalkylthio" radicals. Examples of such radicals include fluoromethylthio, chloromethylthio,

trifluoromethylthio, difluoromethylthio, trifluoroethylthio, fluoroethylthio, tetrafluoroethylthio, pentafluoroethylthio, and fluoropropylthio.

The term "alkyl aryl amino" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, and one aryl radical both  
 5 attached to an amino radical. Examples include N-methyl-4-methoxyaniline, N-ethyl-4-methoxyaniline, and N-methyl-4-trifluoromethoxyaniline.

The terms alkylamino denotes "monoalkylamino" and "dialkylamino" containing one or two alkyl radicals, respectively, attached to an amino radical.

The terms arylamino denotes "monoarylamino" and "diarylamino"  
 10 containing one or two aryl radicals, respectively, attached to an amino radical. Examples of such radicals include N-phenylamino and N-naphthylamino.

The term "aralkylamino", embraces aralkyl radicals attached to an amino radical, where aralkyl is defined as above. The term aralkylamino denotes "monoaralkylamino" and "diaralkylamino" containing one or two  
 15 aralkyl radicals, respectively, attached to an amino radical. The term aralkylamino further denotes "monoaralkyl monoalkylamino" containing one aralkyl radical and one alkyl radical attached to an amino radical.

The term "arylsulfinyl" embraces radicals containing an aryl radical, as defined above, attached to a divalent S(=O) atom. The term "arylsulfinylalkyl"  
 20 denotes arylsulfinyl radicals attached to a linear or branched alkyl radical, of one to ten carbon atoms.

The term "arylsulfonyl", embraces aryl radicals attached to a sulfonyl radical, where aryl is defined as above. "arylsulfonylalkyl", embraces arylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as  
 25 above. The term "heteroarylsulfinyl" embraces radicals containing an heteroaryl radical, as defined above, attached to a divalent S(=O) atom. The term "heteroarylsulfinylalkyl" denotes heteroarylsulfinyl radicals attached to a linear or branched alkyl radical, of one to ten carbon atoms. The term "Heteroarylsulfonyl", embraces heteroaryl radicals attached to a sulfonyl  
 30 radical, where heteroaryl is defined as above. "Heteroarylsulfonylalkyl", embraces heteroarylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "aryloxy" embraces aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy, 4-chloro-3-  
 35 ethylphenoxy, 4-chloro-3-methylphenoxy, 3-chloro-4-ethylphenoxy, 3,4-dichlorophenoxy, 4-methylphenoxy, 3-trifluoromethoxyphenoxy, 3-trifluoromethylphenoxy, 4-fluorophenoxy, 3,4-dimethylphenoxy, 5-bromo-2-

fluorophenoxy, 4-bromo-3-fluorophenoxy, 4-fluoro-3-methylphenoxy, 5,6,7,8-tetrahydronaphthoxy, 3-isopropylphenoxy, 3-cyclopropylphenoxy, 3-ethylphenoxy, 4-*tert*-butylphenoxy, 3-pentafluoroethylphenoxy, and 3-(1,1,2,2-tetrafluoroethoxy)phenoxy.

- 5       The term "aroyl" embraces aryl radicals, as defined above, attached to an carbonyl radical as defined above. Examples of such radicals include benzoyl and toluoyl.

10       The term "aralkanoyl" embraces aralkyl radicals, as defined herein, attached to an carbonyl radical as defined above. Examples of such radicals include, for example, phenylacetyl.

15       The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. More preferred aralkoxy radicals are "lower aralkoxy" radicals having phenyl radicals attached to lower alkoxy radical as described above. Examples of such radicals include benzyloxy, 1-phenylethoxy, 3-trifluoromethoxybenzyloxy, 3-trifluoromethylbenzyloxy, 3,5-difluorobenzyloxy, 3-bromobenzyloxy, 4-propylbenzyloxy, 2-fluoro-3-trifluoromethylbenzyloxy, and 2-phenylethoxy.

20       The term "aryloxyalkyl" embraces aryloxy radicals, as defined above, attached to an alkyl group. Examples of such radicals include phenoxymethyl.

20       The term "haloaryloxyalkyl" embraces aryloxyalkyl radicals, as defined above, wherein one to five halo radicals are attached to an aryloxy group.

25       The term "heteroaroyl" embraces heteroaryl radicals, as defined above, attached to an carbonyl radical as defined above. Examples of such radicals include furoyl and nicotinyl.

25       The term "heteroaralkanoyl" embraces heteroaralkyl radicals, as defined herein, attached to an carbonyl radical as defined above. Examples of such radicals include, for example, pyridylacetyl and furylbutyryl.

30       The term "heteroaralkoxy" embraces oxy-containing heteroaralkyl radicals attached through an oxygen atom to other radicals. More preferred heteroaralkoxy radicals are "lower heteroaralkoxy" radicals having heteroaryl radicals attached to lower alkoxy radical as described above.

35       The term "haloheteroaryloxyalkyl" embraces heteroaryloxyalkyl radicals, as defined above, wherein one to four halo radicals are attached to an heteroaryloxy group.

35       The term "heteroarylamino" embraces heterocyclyl radicals, as defined above, attached to an amino group. Examples of such radicals include pyridylamino.

The term "heteroarylaminomethyl" embraces heteroaryl amino radicals, as defined above, attached to an alkyl group. Examples of such radicals include pyridylmethylamino.

5 The term "heteroaryloxy" embraces heterocyclyl radicals, as defined above, attached to an oxy group. Examples of such radicals include 2-thiophenyloxy, 2-pyrimidyloxy, 2-pyridyloxy, 3-pyridyloxy, and 4-pyridyloxy.

10 The term "heteroaryloxyalkyl" embraces heteroaryloxy radicals, as defined above, attached to an alkyl group. Examples of such radicals include 2-pyridyloxymethyl, 3-pyridyloxyethyl, and 4-pyridyloxymethyl.

The term "aryltio" embraces aryl radicals, as defined above, attached to an sulfur atom. Examples of such radicals include phenyltio.

15 The term "aryltioalkyl" embraces aryltio radicals, as defined above, attached to an alkyl group. Examples of such radicals include phenylthiomethyl.

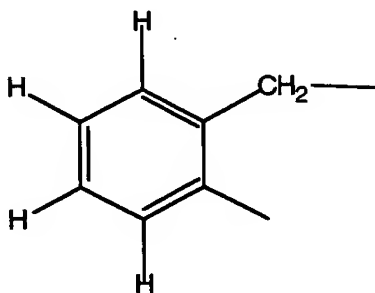
20 The term "alkyltioalkyl" embraces alkyltio radicals, as defined above, attached to an alkyl group. Examples of such radicals include methylthiomethyl. The term "alkoxyalkyl" embraces alkoxy radicals, as defined above, attached to an alkyl group. Examples of such radicals include methoxymethyl.

The term "carbonyl" denotes a carbon radical having two of the four covalent bonds shared with an oxygen atom. The term "carboxy" embraces a hydroxyl radical, as defined above, attached to one of two unshared bonds in a carbonyl group. The term "carboxamide" embraces amino, monoalkylamino, 25 dialkylamino, monocycloalkylamino, alkylcycloalkylamino, and dicycloalkylamino radicals, attached to one of two unshared bonds in a carbonyl group. The term "carboxamidoalkyl" embraces carboxamide radicals, as defined above, attached to an alkyl group. The term "carboxyalkyl" embraces a carboxy radical, as defined above, attached to an alkyl group. The term "carboalkoxy" embraces alkoxy 30 radicals, as defined above, attached to one of two unshared bonds in a carbonyl group. The term "carboaralkoxy" embraces aralkoxy radicals, as defined above, attached to one of two unshared bonds in a carbonyl group. The term "monocarboalkoxyalkyl" embraces one carboalkoxy radical, as defined above, attached to an alkyl group. The term "dicarboalkoxyalkyl" embraces two 35 carboalkoxy radicals, as defined above, attached to an alkylene group. The term "monocyanoalkyl" embraces one cyano radical, as defined above, attached to an alkyl group. The term "dicyanoalkylene" embraces two cyano radicals, as defined

above, attached to an alkyl group. The term "carboalkoxycyanoalkyl" embraces one cyano radical, as defined above, attached to an carboalkoxyalkyl group.

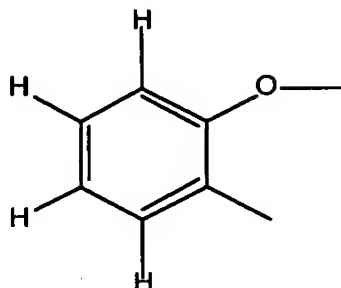
- The term "acyl", alone or in combination, means a carbonyl or thionocarbonyl group bonded to a radical selected from, for example, hydrido, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, alkoxyalkyl, haloalkoxy, aryl, heterocyclyl, heteroaryl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, alkylthio, arylthio, amino, alkylamino, dialkylamino, aralkoxy, arylthio, and alkylthioalkyl. Examples of "acyl" are formyl, acetyl, benzoyl, trifluoroacetyl, phthaloyl, malonyl, nicotinyl, and the like.
- The term "haloalkanoyl" embraces one or more halo radicals, as defined herein, attached to an alkanoyl radical as defined above. Examples of such radicals include, for example, chloroacetyl, trifluoroacetyl, bromopropanoyl, and heptafluorobutanoyl. The term "diacyl", alone or in combination, means having two or more carbonyl or thionocarbonyl groups bonded to a radical selected from, for example, alkylene, alkenylene, alkynylene, haloalkylene, alkoxyalkylene, aryl, heterocyclyl, heteroaryl, aralkyl, cycloalkyl, cycloalkylalkyl, and cycloalkenyl. Examples of "diacyl" are phthaloyl, malonyl, succinyl, adipoyl, and the like.

- The term "benzylidenyl" radical denotes substituted and unsubstituted benzyl groups having attachment points for two covalent bonds. One attachment point is through the methylene of the benzyl group with the other attachment point through an ortho carbon of the phenyl ring. The methylene group is designated for attached to the lowest numbered position. Examples include the base compound benzylidene of structure:



- The term "phenoxyldenyl" radical denotes substituted and unsubstituted phenoxy groups having attachment points for two covalent bonds. One attachment point is through the oxy of the phenoxy group with the other attachment point through an ortho carbon of the phenyl ring. The oxy group is designated for

attached to the lowest numbered position. Examples include the base compound phenoxyldiene of structure:



The term “phosphono” embraces a pentavalent phosphorus attached with two covalent bonds to an oxygen radical. The term “dialkoxyposphono” denotes two alkoxy radicals, as defined above, attached to a phosphono radical with two covalent bonds. The term “diaralkoxyposphono” denotes two aralkoxy radicals, as defined above, attached to a phosphono radical with two covalent bonds. The term “dialkoxyposphonoalkyl” denotes dialkoxyposphono radicals, as defined above, attached to an alkyl radical. The term “diaralkoxyposphonoalkyl” denotes diaralkoxyposphono radicals, as defined above, attached to an alkyl radical.

Said “alkyl”, “alkenyl”, “alkynyl”, “alkanoyl”, “alkylene”, “alkenylene”, “benzylidenyl”, “phenoxyldienyl”, “hydroxyalkyl”, “haloalkyl”, “haloalkylene”, “haloalkenyl”, “alkoxy”, “alkenyloxy”, “alkenyloxyalkyl”, “alkoxyalkyl”, “aryl”, “perhaloaryl”, “haloalkoxy”, “haloalkoxyalkyl”, “haloalkenyloxy”, “haloalkenyloxyalkyl”, “alkylenedioxy”, “haloalkylenedioxy”, “heterocyclyl”, “heteroaryl”, “hydroxyhaloalkyl”, “alkylsulfonyl”, “haloalkylsulfonyl”, “alkylsulfonylalkyl”, “haloalkylsulfonylalkyl”, “alkylsulfinyl”, “alkylsulfinylalkyl”, “haloalkylsulfinylalkyl”, “aralkyl”, “heteroaralkyl”, “perhaloaralkyl”, “aralkylsulfonyl”, “aralkylsulfonylalkyl”, “aralkylsulfinyl”, “aralkylsulfinylalkyl”, “cycloalkyl”, “cycloalkylalkanoyl”, “cycloalkylalkyl”, “cycloalkenyl”, “halocycloalkyl”, “halocycloalkenyl”, “cycloalkylsulfinyl”, “cycloalkylsulfinylalkyl”, “cycloalkylsulfonyl”, “cycloalkylsulfonylalkyl”, “cycloalkoxy”, “cycloalkoxyalkyl”, “cycloalkylalkoxy”, “cycloalkenyloxy”, “cycloalkenyloxyalkyl”, “cycloalkylenedioxy”, “halocycloalkoxy”, “halocycloalkoxyalkyl”, “halocycloalkenyloxy”, “halocycloalkenyloxyalkyl”, “alkylthio”, “haloalkylthio”, “alkylsulfinyl”, “amino”, “oxy”, “thio”, “alkylamino”, “arylamino”, “aralkylamino”, “arylsulfinyl”, “arylsulfinylalkyl”, “arylsulfonyl”, “arylsulfonylalkyl”, “heteroarylsulfinyl”, “heteroarylsulfinylalkyl”,

- “heteroarylsulfonyl”, “heteroarylsulfonylalkyl”, “heteroaryl amino”,  
 “heteroaryl aminoalkyl”, “heteroaryloxy”, “heteroaryloxyalkyl”, “aryloxy”,  
 “aroyl”, “aralkanoyl”, “aralkoxy”, “aryloxyalkyl”, “haloaryloxyalkyl”,  
 “heteroaroyl”, “heteroaralkanoyl”, “heteroaralkoxy”, “heteroaralkoxyalkyl”,  
 5 “arylthio”, “arylthioalkyl”, “alkoxyalkyl”, “acyl” and “diacyl” groups defined  
 above may optionally have 1 to 5 non-hydrido substituents such as perhaloaralkyl,  
 aralkylsulfonyl, aralkylsulfonylalkyl, aralkylsulfinyl, aralkylsulfinylalkyl,  
 halocycloalkyl, halocycloalkenyl, cycloalkylsulfinyl, cycloalkylsulfinylalkyl,  
 cycloalkylsulfonyl, cycloalkylsulfonylalkyl, heteroaryl amino, N-heteroaryl amino-  
 10 N-alkyl amino, heteroaryl aminoalkyl, heteroaryloxy, heteroaryloxyalkyl,  
 haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, heteroaralkoxy,  
 cycloalkoxy, cycloalkenyloxy, cycloalkoxyalkyl, cycloalkylalkoxy,  
 cycloalkenyloxyalkyl, cycloalkylenedioxy, halocycloalkoxy, halocycloalkoxyalkyl,  
 halocycloalkenyloxy, halocycloalkenyloxyalkyl, hydroxy, amino, thio, nitro,  
 15 lower alkyl amino, alkylthio, alkylthioalkyl, aryl amino, aralkyl amino, arylthio,  
 arylthioalkyl, heteroaralkoxyalkyl, alkylsulfinyl, alkylsulfinylalkyl,  
 arylsulfinylalkyl, arylsulfonylalkyl, heteroarylsulfinylalkyl,  
 heteroarylsulfonylalkyl, alkylsulfonyl, alkylsulfonylalkyl, haloalkylsulfinylalkyl,  
 haloalkylsulfonylalkyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl,  
 20 monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoaryl amidosulfonyl,  
 arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl,  
 arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl,  
 alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl,  
 alkyl, alkenyl, alkynyl, alkenyloxy, alkenyloxyalkyl, alkylenedioxy,  
 25 haloalkylenedioxy, cycloalkyl, cycloalkylalkanoyl, cycloalkenyl, lower  
 cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkenyl, haloalkoxy,  
 hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydroxyheteroaralkyl,  
 haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated  
 heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy,  
 30 heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl,  
 carboxyalkyl, carboalkoxy, alkoxycarbonyl, carboaralkoxy, carboxamido,  
 carboxamidoalkyl, cyano, carbohaloalkoxy, phosphono, phosphonoalkyl,  
 diaralkoxyphosphono, and diaralkoxyphosphonoalkyl.

The term “spacer” can include a covalent bond and a linear moiety  
 35 having a backbone of 1 to 7 continuous atoms. The spacer may have 1 to 7

- atoms of a univalent or multi-valent chain. Univalent chains may be constituted by a radical selected from  $=C(H)-$ ,  $=C(R_{17})-$ ,  $-O-$ ,  $-S-$ ,  $-S(O)-$ ,  $-S(O)_2-$ ,  $-NH-$ ,  $-N(R_{17})-$ ,  $-N=$ ,  $-CH(OH)-$ ,  $=C(OH)-$ ,  $-CH(OR_{17})-$ ,  $=C(OR_{17})-$ , and  $-C(O)-$  wherein  $R_{17}$  is selected from alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, aryloxyalkyl, alkoxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, haloalkenyl, haloalkoxyalkyl, perhaloaralkyl, heteroarylalkyl, heteroaryloxyalkyl, heteroarylthioalkyl, and heteroarylalkenyl. Multi-valent chains may consist of a straight chain of 1 or 2 or 3 or 4 or 5 or 6 or 7 atoms or a straight chain of 1 or 2 or 3 or 4 or 5 or 6 atoms with a side chain. The chain may be constituted of one or more radicals selected from: lower alkylene, lower alkenyl,  $-O-$ ,  $-O-CH_2-$ ,  $-S-CH_2-$ ,  $-CH_2CH_2-$ , ethenyl,  $-CH=CH(OH)-$ ,  $-OCH_2O-$ ,  $-O(CH_2)_2O-$ ,  $-NHCH_2-$ ,  $-OCH(R_{17})O-$ ,  $-O(CH_2CHR_{17})O-$ ,  $-OCF_2O-$ ,  $-O(CF_2)_2O-$ ,  $-S-$ ,  $-S(O)-$ ,  $-S(O)_2-$ ,  $-N(H)-$ ,  $-N(H)O-$ ,  $-N(R_{17})O-$ ,  $-N(R_{17})-$ ,  $-C(O)-$ ,  $-C(O)NH-$ ,  $-C(O)NR_{17}-$ ,  $-N=$ ,  $-OCH_2-$ ,  $-SCH_2-$ ,  $S(O)CH_2-$ ,  $-CH_2C(O)-$ ,  $-CH(OH)-$ ,  $=C(OH)-$ ,  $-CH(OR_{17})-$ ,  $=C(OR_{17})-$ ,  $S(O)_2CH_2-$ , and  $-NR_{17}CH_2-$  and many other radicals defined above or generally known or ascertained by one of skill-in-the art. Side chains may include substituents such as 1 to 5 non-hydrido substituents such as perhaloaralkyl, aralkylsulfonyl, aralkylsulfonylalkyl, aralkylsulfinyl, aralkylsulfinylalkyl, halocycloalkyl, halocycloalkenyl, cycloalkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, heteroarylamino, N-heteroarylamino-N-alkylamino, heteroarylaminoalkyl, heteroaryloxy, heteroaryloxyalkyl, haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, cycloalkoxyalkyl, cycloalkylalkoxy, cycloalkenyloxyalkyl, cycloalkylenedioxy, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxy, halocycloalkenyloxyalkyl, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, arylthioalkyl, heteroaralkoxyalkyl, alkylsulfinyl, alkylsulfinylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, heteroarylsulfinylalkyl,



heteroarylsulfonylalkyl, alkylsulfonyl, alkylsulfonylalkyl, haloalkylsulfinylalkyl, haloalkylsulfonylalkyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, 5 diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkenyloxy, alkenyloxyalkyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower 10 cycloalkenylalkyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboxyalkyl, carboalkoxy, 15 carboaralkoxy, carboxamido, carboxamidoalkyl, cyano, carbohaloalkoxy, phosphono, phosphonoalkyl, diaralkoxyphosphono, and diaralkoxyphosphonoalkyl.

Chiral compounds of the present invention have a hydroxyl group substituent on a chiral carbon of the alkanol and propanol compounds of the 20 present invention specifically in the R-stereoisomeric configuration based on the Cahn-Ingold-Prelog convention for stereoisomeric carbon atoms. The R-stereoisomeric configuration compounds of the present invention may optionally have one or more additional chiral carbons present in each compound. The R-stereoisomeric configuration compounds of the present invention can exist in 25 tautomeric, geometric, and other stereoisomeric forms. The present invention having a hydroxyl group substituent on a chiral carbon of the alkanol and propanol compounds in the R-stereoisomeric configuration contemplates all such forms of said invented compounds, including cis- and trans-geometric isomers, E- and Z-geometric isomers, diastereomers, and other mixtures thereof, as falling within the 30 scope of the invention. Pharmaceutically acceptable salts of such tautomeric, geometric or stereoisomeric forms are also included within the invention. The standard definitions for the Cahn-Ingold-Prelog convention and stereochemical system can be found in Pure Applied Chemistry, 1976, Vol. 45, pages 15-30 and Cahn et al., Angewandte Chemie International Edition English, 1966, Vol. 5, 35 pages 385-415.

The terms "cis" and "trans" denote a form of geometric isomerism in which two carbon atoms connected by a double bond will each have a

hydrogen atom on the same side of the double bond ("cis") or on opposite sides of the double bond ("trans").

Some of the compounds described contain alkenyl groups, and are meant to include both cis and trans or "E" and "Z" geometric forms.

5           Some of the compounds described contain one or more stereocenters in addition to said hydroxyl group substituent on a chiral carbon of the alkanol and propanol compounds in the R-stereoisomeric configuration and are meant to include R, S, and mixtures of R and S forms for each additional stereocenter present.

10           Some of the compounds described herein may contain one or more ketonic or aldehydic carbonyl groups or combinations thereof alone or as part of a heterocyclic ring system. Such carbonyl groups may exist in part or principally in the "keto" form and in part or principally as one or more "enol" forms of each aldehyde and ketone group present. Compounds of the present  
15           invention having aldehydic or ketonic carbonyl groups are meant to include both "keto" and "enol" tautomeric forms.

          Some of the compounds described herein may contain one or more amide carbonyl groups or combinations thereof alone or as part of a heterocyclic ring system. Such carbonyl groups may exist in part or principally  
20           in the "keto" form and in part or principally as one or more "enol" forms of each amide group present. Compounds of the present invention having amidic carbonyl groups are meant to include both "keto" and "enol" tautomeric forms. Said amide carbonyl groups may be both oxo ( $C=O$ ) and thiono ( $C=S$ ) in type.

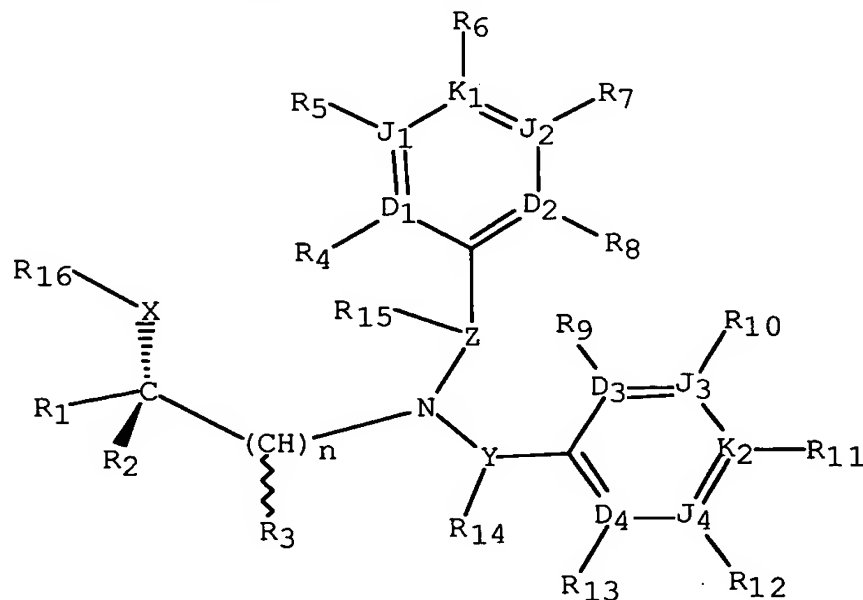
          Some of the compounds described herein may contain one or more  
25           imine or enamine groups or combinations thereof. Such groups may exist in part or principally in the "imine" form and in part or principally as one or more "enamine" forms of each group present. Compounds of the present invention having said imine or enamine groups are meant to include both "imine" and "enamine" tautomeric forms.

30           The following general synthetic sequences are useful in making the present invention. Abbreviations used in the schemes are as follows: "AA" represents amino acids, "BINAP" represents 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, "Boc" represents tert-butyloxycarbonyl, "BOP" represents benzotriazol-1-yl-oxy-tris-(dimethylamino), "bu" represents butyl, "dba"  
35           represents dibenzylideneacetone, "DCC" represents 1,3-dicyclohexylcarbodiimide, "DIBAH" represents diisobutylaluminum hydride, "DIPEA" represents diisopropylethylamine, "DMF" represents

dimethylformamide, "DMSO" represents dimethylsulfoxide, "Fmoc" represents 9-fluorenylmethoxycarbonyl, "LDA" represents lithium diisopropylamide, "PHTH" represents a phthaloyl group, "pnZ" represents 4-nitrobenzyloxycarbonyl, "PTC" represents a phase transfer catalyst, "p-TsOH" represents paratoluenesulfonic acid, "TBAF" represents tetrabutylammonium fluoride, "TBTU" represents 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate, "TEA" represents triethylamine, "TFA" represents trifluoroacetic acid, "THF" represents tetrahydrofuran, "TMS" represents trimethylsilyl, and "Z" represents benzyloxycarbonyl.

The present invention comprises a pharmaceutical composition comprising a therapeutically-effective amount of a compound of Formulas I-H, I-HP, I-C, I-CP, I-HPC, Cyclo I-H, Cyclo I-C, and Cyclo I-CP in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent.

The present invention also comprises a treatment and prophylaxis of coronary artery disease and other CETP-mediated disorders in a subject, comprising administering to the subject having such disorder a therapeutically-effective amount of a compound of Formula I-H:



(I-H)

or a pharmaceutically-acceptable salt thereof, wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$ ,  $R_8$ ,  $R_9$ ,  $R_{10}$ ,  $R_{11}$ ,  $R_{12}$ ,  $R_{13}$ ,  $R_{14}$ ,  $R_{15}$ ,  $R_{16}$ , X, Y, and Z are as defined above for the compounds of Formula I-H.

As a further embodiment, compounds of the present invention of Formulas I-H, I-HP, I-C, I-CP, I-HPC, Cyclo I-H, Cyclo I-C, and Cyclo I-CP or a pharmaceutically-acceptable salt thereof as defined above comprise a treatment and prophylaxis of coronary artery disease and other CETP-mediated disorders in a subject, comprising administering to the subject having such disorder a therapeutically-effective amount of compounds I-H, I-HP, I-C, I-CP, I-HPC, Cyclo I-H, Cyclo I-C, and Cyclo I-CP of the present invention or a pharmaceutically-acceptable salt thereof.

Compounds of Formulas I-H, I-HP, I-C, I-CP, I-HPC, Cyclo I-H, Cyclo I-C, and Cyclo I-CP are capable of inhibiting activity of cholesteryl ester transfer protein (CETP), and thus could be used in the manufacture of a medicament, a method for the prophylactic or therapeutic treatment of diseases mediated by CETP, such as peripheral vascular disease, hyperlipidaemia, hypercholesterolemia, and other diseases attributable to either high LDL and low HDL or a combination of both, or a procedure to study the mechanism of action of the cholesteryl ester transfer protein (CETP) to enable the design of better inhibitors. The compounds of Formula I-H would be also useful in prevention of cerebral vascular accident (CVA) or stroke.

Also included in the family of compounds of Formula I-H, I-HP, I-C, I-CP, I-HPC, Cyclo I-H, Cyclo I-C, and Cyclo I-CP are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I-H may be prepared from inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethylsulfonic, benzenesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic, galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula V-H include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or

organic salts made from N,N'-dibenzylethylenediamine, choline, chloroprocaine, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procain. All of these salts may be prepared by conventional means from the corresponding compound of Formula I-H by reacting, for example, the appropriate acid or base with the compound of Formula I-H.

Also embraced within this invention is a class of pharmaceutical compositions comprising the active compounds of Formula I-H in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The active compounds and composition may, for example, be administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

The amount of therapeutically active compounds which are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely.

The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 2000 mg, and preferably in the range of about 0.5 to 500 mg. A daily dose of about 0.01 to 100 mg/kg body weight, and preferably between about 0.5 and about 20 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

The compounds may be formulated in topical ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to

15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base.

Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may

5 include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration  
10 enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules  
15 through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

20 The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is  
25 also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present  
30 invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion  
35 formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic

alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the  
5 properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

For therapeutic purposes, the active compounds of this combination invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered *per os*, the compounds  
10 may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such  
15 capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or  
20 granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely  
25 known in the pharmaceutical art.

The present invention further comprises a process for the preparation of (R)-chiral compounds of Formulas I-H, I-HP, I-C, I-CP, I-HPC, Cyclo I-H, Cyclo I-C, and Cyclo I-CP by reacting suitable secondary amines with (R)-chiral forms of alcohols, epoxides, and cyclic sulfate esters.

30 The present invention also comprises a process for the preparation of (R)-chiral compounds of Formulas I-H, I-HP, I-C, I-CP, I-HPC, Cyclo I-H, Cyclo I-C, and Cyclo I-CP by reacting a suitable secondary amine with a substantially stoichiometric amount of a (R)-chiral epoxide in the presence of a transition metal-based salt.

35 The present invention also comprises a process for the preparation of (R)-chiral precursor compounds useful in the preparation of compounds of Formulas I-H, I-HP, I-C, I-CP, I-HPC, Cyclo I-H, Cyclo I-C, and Cyclo I-

CP by reacting a suitable primary amine with a substantially stoichiometric amount of a (R)-chiral epoxide with or without the presence of an added transition metal-based compound.

5 All mentioned references are incorporated by reference as if here written.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

## 10 GENERAL SYNTHETIC PROCEDURES

The compounds of the present invention can be synthesized, for example, according to the following procedures of Schemes 1 through 58 below, wherein the substituents are as defined for Formulas I-H, I-HP, I-C, I-CP, I-HPC, Cyclo I-H, Cyclo I-C, and Cyclo I-CP above except where further noted.

Synthetic Schemes 1 and 2 shows the preparation of compounds of formula XIII ("Generic Secondary Amines") which are intermediates in the preparation of the compounds of the present invention corresponding to  
 20 Formula I-H ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-alkanols"), Formula I-HP ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated I-Substitutedamino-2-propanols"), Formula I-HPC ("Polycyclic Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols"), Formula I-C ("Polycyclic Phenyl (R)-Chiral  
 25 Halogenated 1-Substitutedamino-(n+1)-Alkanols"), and Formula I-CP ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") wherein A and Q are independently aryl and heteroaryl. Schemes 1 and 2, taken together, prepare 1-substitutedamino-2-alkanols of the present invention by addition of a halogenated, oxygen containing precursor to a secondary  
 30 amine to introduce an oxy containing alkyl group wherein the two groups making up the secondary amine both are made up of aromatic groups or both groups contain aromatic rings wherein said aromatic rings maybe 0 to 2 aryl rings and 0 to 2 heteroaryl rings.

The "Generic Imine" corresponding to Formula XII can be prepared  
 35 through dehydration techniques generally known in the art and the preferred technique depending on the nature of "Generic Amine-I" of Formula X by



reacting it with the "Generic Carbonyl Compound" of Formula XI. For example, when Z is a covalent bond, methylene, methine substituted with another substituent, ethylene, or another substituent as defined in Formula I-H, the two reactants (X and XI) react by refluxing them in an aprotic solvent, such as hexane, toluene, cyclohexane, benzene, and the like, using a Dean-Stark type trap to remove water. After about 2-8 hours or until the removal of water is complete, the aprotic solvent is removed *in vacuo* to yield the "Generic Imine" of Formula XII. Alternately, when Z is an oxygen, the "Generic Imine" is an oxime derivative. Oxime type "Generic Imine" compounds are readily prepared from the corresponding O-substituted hydroxylamine and the appropriate aldehyde or ketone type "Generic Carbonyl Compound". Suitable procedures are described by Shriner, Fuson, and Curtin in The Systematic Identification of Organic Compounds, 5th Edition, John Wiley & Sons and by Fieser and Fieser in Reagents for Organic Synthesis, Volume 1, John Wiley & Sons, which are incorporated herein by reference. Alternately, when Z is a nitrogen, the "Generic Imine" is a hydrazone derivative. Hydrazone type "Generic Imine" compounds are readily prepared from the corresponding hydrazine and the appropriate aldehyde or ketone type "Generic Carbonyl Compound". Suitable procedures for forming the hydrazone imines are also described by Shriner, Fuson, and Curtin in The Systematic Identification of Organic Compounds, 5th Edition, John Wiley & Sons, and by Fieser and Fieser in Reagents for Organic Synthesis, Volume 1, John Wiley & Sons, which are incorporated herein by reference.

Scheme 1 shows the preparation of "Generic Imine" compounds in which the amine functionality is bonded to Z; Z is bonded to A; and Y is bonded to Q. One of skill in the art will recognize that A and Q as defined can be structurally interchanged to prepare "Generic Imine" compounds with similar, identical or different structures.

The "Generic Secondary Amines" of Formula XIII can be prepared from the corresponding "Generic Imine" of Formula XII in several ways.

For example, in one synthetic scheme (Reduction Method-1), which is preferred when Z is a nitrogen, the "Generic Imine" hydrazone of Formula XII is partially or completely dissolved in lower alkanols such as ethanol or like solvent containing sufficient organic acid such as acetic acid or mineral acid such as HCl or sulfuric acid to neutralize the hydrazone as described in WO Patent Application No.9738973, Swiss Patent CH 441366 and U. S. Patent Nos. 3359316 and 3334017, which are incorporated herein by reference. The

resulting mixture is then hydrogenated at 0-100°C, more preferably 20-50°C, and most preferably between 20-30°C and pressures of 10-200 psi hydrogen or more preferably between 50-70 psi hydrogen in the presence of a noble metal catalyst such as PtO<sub>2</sub>. The mixture is cooled, and a base such as sodium carbonate or sodium hydroxide added until the solution is neutral to just alkaline (pH 6-8).

Isolation of the desired product can be accomplished, for example, by removing the ethanol, adding water, and extracting the aqueous-organic mixture twice with a solvent, such as diethyl ether or methylene chloride, that is immiscible with water. The combined solvent extract is washed with saturated brine, dried with a drying agent such as anhydrous magnesium sulfate, and concentrated *in vacuo* to yield the "Generic Secondary Amines" hydrazine of Formula XIII. If needed the "Generic Secondary Amines" hydrazine can be further purified by crystallization, distillation at reduced pressure, or liquid chromatography.

In another synthetic scheme (Reduction Method-2), which is preferred when Z is a single bond or carbon, the "Generic Imine" of Formula XII is slurried in a lower alcohol such as ethanol, methanol or like solvent at 0-10°C and solid sodium borohydride is added in batches over 5-10 minutes at 0-10°C with stirring. The reaction mixture is stirred below 10°C for 30-90 minutes and then is warmed gradually to 15-30°C. After about 1-10 hours, the mixture is cooled and acid is added until the aqueous layer was just acidic (pH 5-7).

Isolation of the desired product can be accomplished, for example, by extracting the aqueous layer twice with a solvent, such as diethyl ether or methylene chloride, that is immiscible with water. The combined solvent extract is washed with saturated brine, dried with a drying agent such as anhydrous MgSO<sub>4</sub>, and concentrated *in vacuo* to yield the "Generic Secondary Amines" amine, aniline, or amine of Formula XIII. If needed the "Generic Secondary Amines" amine, aniline, or amine derivative can be further purified by crystallization, distillation at reduced pressure, or liquid chromatography.

In yet another synthetic scheme (Reduction Method-3), which is preferred when Z is an oxygen, the "Generic Imine" oxime of Formula XII is slurried in a lower alcohol solvent such methanol or like solvent at 0-10°C and

acidified to a pH less than 4. Solid sodium cyanoborohydride is added in batches over 30-90 minutes at 0-20°C with stirring and addition of a suitable organic or mineral acid to keep the pH at or below 4. The reaction mixture is stirred and warmed gradually to about 20-25°C. After about 1-10 hours, the mixture is cooled and base added until the mixture was just slightly alkaline.

Isolation of the desired product can be accomplished, for example, by removing the methanol or other low boiling solvent *in vacuo*. The residue is slurried with water and aqueous-organic mixture is extracted twice with a solvent, such as diethyl ether or methylene chloride, that is immiscible with water. The combined solvent extract is washed with saturated brine, dried with a drying agent such as anhydrous  $\text{MgSO}_4$ , and concentrated *in vacuo* to yield the "Generic Secondary Amines" hydroxylamine of Formula XIII. If needed the "Generic Secondary Amines" hydroxylamine can be further purified by crystallization, distillation at reduced pressure, or liquid chromatography.

The "Generic Secondary Amines" of Formula XIII can also be prepared, according to Scheme 1 by two alkylation procedures based on the nucleophilic substitution of bromides by amines. In one procedure, "Generic Amine-1" of Formula X is reacted with "Generic Bromide-1" of Formula XXI. In another alkylation procedure, "Generic Amine-2" of Formula XXII is reacted together with "Generic Bromide-2" of Formula XXIII.

In one synthetic alkylation scheme (Alkylation Method-1), a "Generic Amine-1" of Formula X is reacted with a "Generic Bromide-2" of Formula XXIII as described in Vogel's Textbook of Practical Organic Chemistry, Fifth Edition, 1989, pages 902 to 905 and references cited therein all of which are incorporated herein by reference. In this procedure, the "Generic Amine-1" is placed in a reaction vessel equipped with a reflux condenser with the capability to either cool or heat the vessel as dictated by the reaction. A suitable "Generic Amine-1" will be selected from primary amine and primary aromatic amine classes of compounds. Cooling may be needed and used should the reaction prove strongly exothermic. Heating may be needed and used to drive the reaction to completion. A suitable solvent may also be used to dissolve the "Generic Amine-1". Suitable solvents are hydrocarbons such as toluene, hexane, xylene, and cyclohexane, ethers, amides such as dimethylformamide, esters such as ethyl acetate, ketones such as acetone, and nitriles such as acetonitrile or mixtures of two or more of these solvents. A suitable base is

also added to the reaction vessel. Suitable bases include cesium carbonate, calcium carbonate, sodium carbonate and sodium bicarbonate. The base will normally be added in at least a stoichmetric quantity compared to the "Generic Amine-1" so as to neutralize liberated acid as it forms.

- 5           The "Generic Bromide-1" of Formula XXI is then added to the reaction vessel in portions so as to minimize the rate of heat evolution and minimize the concentration of the "Generic Bromide-1". The "Generic Bromide-1" will be selected from primary and secondary organic alkyl and substituted alkyl halide compounds. The halide will preferrably be a bromide although iodides and  
10 chlorides may also be generally used. One of skill in the art will also be able to readily select and utilize organic alkyl and substituted alkyl compounds containing readily displaceable primary and secondary groups such as tosylates, mesylates, triflates, and the like. Alternately, the halides can be generally prepared from the corresponding alcohols by reaction with, for  
15 example, concentrated hydrohalic acids such as HBr or by reaction with phosphorus trihalides such as PBr<sub>3</sub> as described in Fieser and Fieser in Reagents for Organic Synthesis, Volume 1, John Wiley & Sons, which are incorporated herein by reference. The appropriate alcohols can be converted to tosylates, mesylates, and triflates using procedures described below.
- 20           Addition of the "Generic Bromide-1" is carried out over a period of a few minutes to several hours at temperatures between 0 and 150 °C. Preferrably, the addition will take 30-120 minutes at a temperature of 0 to 50 °C. The reaction can be stirred until completion. Completion can be monitored, for example, spectroscopically using nuclear magnetic resonance  
25 or chromatographically using thin layer, liquid, or gas chromatographic procedures. If the reaction does not proceed to completion, the reactants may be heated until completion is obtained and verified.

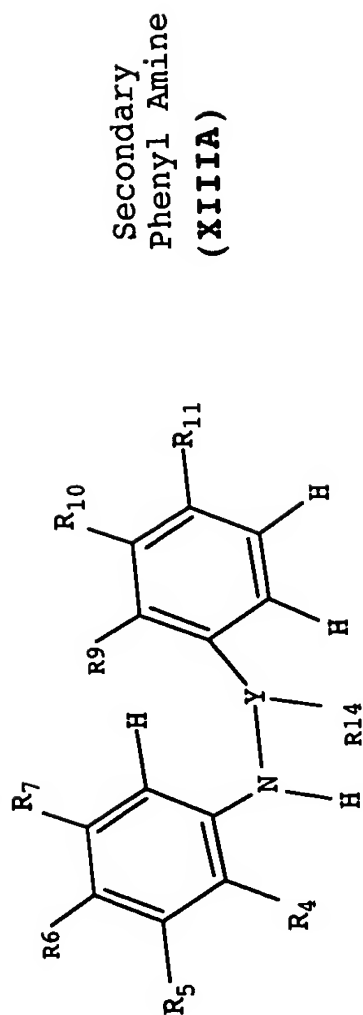
- Isolation of the desired product can be accomplished, for example, when a water immiscible solvent was used for the reaction, by adding water to  
30 the finished reaction. Additional base such as sodium carbonate can be added to ensure the reaction is basic (pH of 9 to 11). The organic layer containing the "Generic Secondary Amine" is washed with saturated brine, dried with a drying agent such as anhydrous MgSO<sub>4</sub>, and concentrated *in vacuo* to yield the "Generic Secondary Amine" amine, aniline, or amine of Formula XIII. If  
35 needed the "Generic Secondary Amine" amine, aniline, or amine derivative can

be further purified by crystallization, distillation at reduced pressure, or liquid chromatography.

In a second synthetic alkylation scheme (Alkylation Method-2), a "Generic Amine-2" of Formula XXII is reacted with a "Generic Bromide-2" of Formula XXIII in a method employing palladium catalyzed carbon-nitrogen bond formation. Suitable procedures for this conversion are described in Wagaw and Buchwald, J. Org. Chem.(1996), 61, 7240-7241, Wolfe, Wagaw and Buchwald, J. Am. Chem. Soc. (1996), 118, 7215-7216, and Wolfe and Buchwald, Tetrahedron Letters (1997), 38(36), 6359-6362 and references cited therein all of which are incorporated herein by reference. The preferred "Generic Bromide-2" of Formula XXIII are generally aryl bromides, aryl triflates, and heteroaryl bromides.

The "Generic Amine-1" and "Generic Amine-2" amines, hydroxylamines, and hydrazines, the "Generic Carbonyl Compound" aldehydes, ketones, hydrazones, and oximes, and "Generic Bromide-1" and "Generic Bromide-2" halides, tosylates, mesylates, triflates, and precursor alcohols required to prepare the "Generic Secondary Amine" compounds are available from commercial sources, can be prepared by one skilled in the art from published procedures, and/or can be obtained using specific procedures shown in Schemes 42, 43, and 44. Commercial sources include but are not limited to Aldrich Chemical, TCI-America, Lancaster-Synthesis, Oakwood Products, Acros Organics, and Maybridge Chemical. Disclosed procedures for "Generic Amine" amines, hydroxylamines, and hydrazines include Sheradsky and Nov, J. Chem. Soc., Perkin Trans.1 (1980), (12), 2781-6; Marcoux, Doye, and Buchwald, J. Am. Chem. Soc. (1997), 119, 1053-9; Sternbach and Jamison, Tetrahedron Lett. (1981), 22(35), 3331-4; U. S. Patent No. 5306718; EP No. 314435; WO No. 9001874; WO No. 9002113; JP No. 05320117; WO No. 9738973; Swiss Patent No. CH 441366; U. S. Patents Nos. 3359316 and 3334017; and references cited therein which are incorporated herein by reference. Representative specific "Generic Secondary Amine" of Formula XIII compounds useful for the preparation of compounds of the present invention are listed in Tables 3, 4, and 5.

Table 3. Structure of "Secondary Phenyl Amine" Reagents.



Reagent Number	<u>R<sub>4</sub></u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>
1N	H	phenoxy	H	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	H	CH	H
2N	H	OCF <sub>3</sub>	H	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	H	CH	H
3N	F	H	H	F	H	OCF <sub>2</sub> CF <sub>2</sub> H	H	CH	H
4N	H	F	H	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	H	CH	H
5N	H	phenoxy	H	H	H	OCF <sub>3</sub>	H	CH	H
6N	H	OCF <sub>3</sub>	H	H	H	OCF <sub>3</sub>	H	CH	H

Table 3. (continued) Structure of "Secondary Phenyl Amine" Reagents.

<u>Reagent Number</u>	<u>R<sub>4</sub></u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>
7N	H	H	phenyl	H	H	OCF <sub>3</sub>	H	CH	H
8N	H	phenyl	H	H	H	OCF <sub>3</sub>	H	CH	H
9N	H	H	H	H	H	OCF <sub>3</sub>	H	CH	H
10N	H	Br	H	H	H	OCF <sub>3</sub>	H	CH	H
11N	H	CF <sub>3</sub>	F	H	H	CF <sub>3</sub>	H	CH	H
12N	H	CH <sub>3</sub>	H	H	H	CF <sub>3</sub>	H	CH	H
13N	H	CF <sub>3</sub>	H	H	H	CF <sub>3</sub>	H	CH	H
14N	H	CH <sub>3</sub>	H	H	H	OCF <sub>3</sub>	H	CH	H
15N	H	F	F	H	H	OCF <sub>3</sub>	H	CH	H
16N	H	Br	H	H	H	CF <sub>3</sub>	H	CH	H
17N	H	CF <sub>3</sub>	F	H	H	OCF <sub>3</sub>	H	CH	H
18N	H	F	H	H	H	OCF <sub>3</sub>	H	CH	H

Table 3. (continued) Structure of "Secondary Phenyl Amine" Reagents.

<u>Reagent Number</u>	<u>R<sub>4</sub></u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>
19N	H	Cl	H	H	H	OCF <sub>3</sub>	H	CH	H
20N	H	F	H	H	H	CF <sub>3</sub>	H	CH	H
21N	H	F	F	H	H	CF <sub>3</sub>	H	CH	H
22N	H	Cl	H	H	H	CF <sub>3</sub>	H	CH	H
23N	H	F	H	H	H	phenoxy	H	CH	H
24N	H	CF <sub>3</sub>	Cl	H	H	CH <sub>3</sub>	H	CH	H
25N	H	CF <sub>3</sub>	F	H	H	CH <sub>3</sub>	H	CH	H
26N	H	H	H	H	H	CF <sub>3</sub>	H	CH	H
27N	F	F	H	H	H	CF <sub>3</sub>	H	CH	H
28N	H	H	OCH <sub>3</sub>	H	H	CF <sub>3</sub>	H	CH	H
29N	H	F	F	H	H	CH <sub>3</sub>	H	CH	H
30N	H	OCH <sub>3</sub>	H	H	H	CH <sub>3</sub>	H	CH	H



Table 3. (continued) Structure of "Secondary Phenyl Amine" Reagents.

<u>Reagent Number</u>	<u>R<sub>4</sub></u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>
31N	H	H	CH <sub>3</sub>	H	H	H	H	CH	H
32N	H	Cl	H	H	H	H	H	CH	H
33N	H	F	H	H	H	F	H	CH	H
34N	H	H	OCH <sub>3</sub>	H	H	CH <sub>3</sub>	H	CH	H
35N	H	H	H	H	H	H	H	CH	H
36N	H	H	CH <sub>3</sub>	H	H	CH <sub>3</sub>	H	CH	H
37N	H	H	Cl	H	H	H	H	CH	H
38N	H	F	H	H	H	3-CF <sub>3</sub> -phenoxy	H	CH	H
39N	H	F	H	H	H	4-CH <sub>3</sub> O-phenoxy	H	CH	H
40N	H	F	H	H	H	4-Cl-phenoxy	H	CH	H
41N	H	F	H	H	H	H	H	CH	H
42N	H	F	H	H	H	CH <sub>3</sub>	H	CH	H
43N	H	F	H	F	H	CH <sub>3</sub>	H	CH	H
44N	F	F	H	H	H	CH <sub>3</sub>	H	CH	H

Table 3. (continued) Structure of "Secondary Phenyl Amine" Reagents.

<u>Reagent Number</u>	<u>R<sub>4</sub></u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>
45N	H	Cl	H	H	H	CH <sub>3</sub>	H	CH	H
46N	H	CH <sub>3</sub>	H	H	H	CH <sub>3</sub>	H	CH	H
48N	H	H	CH <sub>3</sub>	H	H	CF <sub>3</sub>	H	CH	H
51N	H	H	CH <sub>3</sub>	H	H	F	H	CH	H
52N	H	CF <sub>3</sub>	H	H	H	F	H	CH	H
53N	H	CF <sub>3</sub>	H	H	H	CH <sub>3</sub>	H	CH	H
54N	H	OCH <sub>3</sub>	H	H	H	CF <sub>3</sub>	H	CH	H
56N	H	H	CH <sub>3</sub>	H	H	CF <sub>3</sub>	H	CH	H
57N	H	phenoxy	H	H	H	H	OCF <sub>3</sub>	CH	H
58N	H	H	H	H	H	H	OCF <sub>3</sub>	CH	H
59N	H	OCF <sub>3</sub>	H	H	H	H	OCF <sub>3</sub>	CH	H
60N	H	CF <sub>3</sub>	F	H	H	H	CF <sub>3</sub>	CH	H

Table 3. (continued) Structure of "Secondary Phenyl Amine" Reagents.

<u>Reagent Number</u>	<u>R<sub>4</sub></u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>
61N	H	H	OCH <sub>3</sub>	H	H	H	CF <sub>3</sub>	CH	H
62N	H	CH <sub>3</sub>	H	H	H	H	CF <sub>3</sub>	CH	H
63N	H	Cl	H	H	H	H	CF <sub>3</sub>	CH	H
64N	H	CF <sub>3</sub>	H	H	H	H	OCF <sub>3</sub>	CH	H
65N	H	F	H	H	H	H	OCF <sub>3</sub>	CH	H
66N	H	F	H	F	H	H	OCF <sub>3</sub>	CH	H
67N	H	Br	H	H	H	H	OCF <sub>3</sub>	CH	H
68N	H	Cl	H	H	H	H	OCF <sub>3</sub>	CH	H
69N	H	F	F	H	H	H	OCF <sub>3</sub>	CH	H
70N	H	F	H	H	H	H	phenyl	CH	H
71N	H	CH <sub>3</sub>	H	H	H	H	OCF <sub>3</sub>	CH	H
72N	H	F	F	H	H	H	CF <sub>3</sub>	CH	H

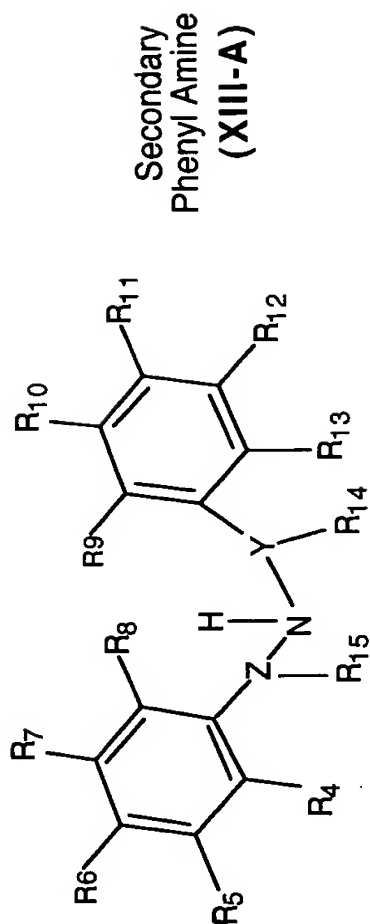
Table 3. (continued) Structure of "Secondary Phenyl Amine" Reagents.

<u>Reagent Number</u>	<u>R<sub>4</sub></u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>
73N	H	Cl	H	H	H	H	CH <sub>3</sub>	CH	H
74N	H	OCH <sub>3</sub>	H	H	H	H	CH <sub>3</sub>	CH	H
75N	H	F	H	H	H	H	CH <sub>3</sub>	CH	H
76N	F	F	H	H	H	H	OCF <sub>3</sub>	CH	H
78N	H	H	OCH <sub>3</sub>	H	H	H	CH <sub>3</sub>	CH	H
79N	H	H	CH <sub>3</sub>	H	H	H	CH <sub>3</sub>	CH	H
80N	H	CH <sub>3</sub>	H	H	H	H	CH <sub>3</sub>	CH	H
82N	H	F	F	H	H	H	CH <sub>3</sub>	CH	H
83N	H	F	H	F	H	H	CH <sub>3</sub>	CH	H
84N	F	F	H	H	H	H	CH <sub>3</sub>	CH	H
85N	F	CF <sub>3</sub>	H	H	H	H	CH <sub>3</sub>	CH	H
86N	H	H	CH <sub>3</sub>	H	H	H	CF <sub>3</sub>	CH	H

Table 3. (continued) Structure of "Secondary Phenyl Amine" Reagents.

<u>Reagent Number</u>	<u>R<sub>4</sub></u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>
88N	H	CF <sub>3</sub>	H	H	H	H	CH <sub>3</sub>	CH	H
90N	H	H	CF <sub>3</sub>	H	H	H	CH <sub>3</sub>	CH	H
92N	H	CF <sub>3</sub>	F	H	H	H	CH <sub>3</sub>	CH	H

Table 4. Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent; R<sub>4</sub> and R<sub>13</sub> equal H).



<u>R<sub>g</sub>t.</u> <u>N<sub>o</sub>.</u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
93N	Br	H	H		CH	H		H	H	OCF <sub>3</sub>	-O-	R <sub>g</sub> +R <sub>9</sub>
94N	OCF <sub>3</sub>	H	H		CH	H		H	H	OCF <sub>3</sub>	-	R <sub>g</sub> +R <sub>9</sub>
95N	Br	H	H		C		H	OCF <sub>3</sub>	H	H	=CH-	R <sub>g</sub> +R <sub>14</sub>
96N	OH	OH	H	H	CH	H	H	C <sub>6</sub> H <sub>5</sub> O	H	H	none	none
97N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OH	OH	H	none	none

Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent;R<sub>4</sub> and R<sub>13</sub> equal H).

<u>R<sub>gnt</sub></u> <u>No.</u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
98N	3-pyridyl	H	H	H	CH	H	H	CF <sub>3</sub>	H	H	none	none
99N	SO <sub>2</sub> N (CH <sub>3</sub> ) <sub>2</sub>	H	H	H	CH	H	H	OCF <sub>3</sub>	H	H	none	none
100N	SO <sub>2</sub> CH <sub>3</sub>	H	H	H	CH	H	H	OCF <sub>3</sub>	H	H	none	none
101N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	C <sub>6</sub> H <sub>5</sub> O	H	H	none	none
102N	CF <sub>3</sub> O	H	H	H	CH	H	H	C <sub>6</sub> H <sub>5</sub> O	H	H	none	none
103N	C <sub>6</sub> H <sub>5</sub>	H	H	H	CH	H	H	C <sub>6</sub> H <sub>5</sub> O	H	H	none	none
104N	H	C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	C <sub>6</sub> H <sub>5</sub> O	H	H	none	none
105N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	4-Cl-C <sub>6</sub> H <sub>4</sub> O	H	H	none	none
106N	CF <sub>3</sub> O	H	H	H	CH	H	H	4-Cl-C <sub>6</sub> H <sub>4</sub> O	H	H	none	none
107N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	3,4-Cl-C <sub>6</sub> H <sub>3</sub> O	H	H	none	none

Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent; R<sub>4</sub> and R<sub>13</sub> equal H).

<u>Rgnt.</u> <u>No.</u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
108N	CF <sub>3</sub> O	H	H	H	CH	H	H	3,4-Cl-C <sub>6</sub> H <sub>3</sub> O	H	H	none	none
109N	CF <sub>3</sub> O	H	H	H	CH	H	H	3,5-Cl-C <sub>6</sub> H <sub>3</sub> O	H	H	none	none
110N	CF <sub>3</sub> O	H	H	H	CH	H	H	3-CH <sub>3</sub> O- C <sub>6</sub> H <sub>4</sub> O	H	H	none	none
111N	CF <sub>3</sub> O	H	H	H	CH	H	H	H	3-CH <sub>3</sub> O- C <sub>6</sub> H <sub>4</sub> O	H	none	none
112N	CF <sub>3</sub> O	H	H	H	CH	H	H	3-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> O	H	H	none	none
113N	CF <sub>3</sub> O	H	H	H	CH	H	H	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub> O	H	H	none	none
114N	CF <sub>3</sub> O	H	H	H	CH	H	H	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub> O	CH <sub>3</sub> O	H	none	none
115N	CF <sub>3</sub> O	H	H	H	CH	H	H	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub> O	C <sub>6</sub> H <sub>5</sub> - CH <sub>2</sub> O	H	none	none



Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent; R<sub>4</sub> and R<sub>13</sub> equal H).


<u>R<sub>g</sub>t.</u> <u>N<sub>o</sub>.</u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
116N	CF <sub>3</sub> O	H	H	H	CH	H	H	ethoxy	H	H	none	none
117N	CF <sub>3</sub> O	H	H	H	CH	H	H	CH <sub>3</sub> CO <sub>2</sub>	H	H	none	none
118N	CF <sub>3</sub> O	H	H	H	CH	H	H	HOCH <sub>2</sub> - CH <sub>2</sub> O	H	H	none	none
119N	CF <sub>3</sub> O	H	H	H	CH	H	H		H	H	none	none
120N	CF <sub>3</sub> O	H	H	H	CH	H	H	R <sub>10</sub> +R <sub>11</sub> =OCH <sub>2</sub> O	H	H	none	none
121N	CF <sub>3</sub> O	H	H	H	CH	H	H	R <sub>10</sub> +R <sub>11</sub> =OCH <sub>2</sub> CH <sub>2</sub> O	H	H	none	none
122N	CF <sub>3</sub> O	H	H	H	CH	H	H	CH <sub>3</sub> O	CH <sub>3</sub> O	H	none	none
123N	CF <sub>3</sub> O	H	H	H	CH	H	H	ethoxy	CH <sub>3</sub> O	H	none	none
124N	CF <sub>3</sub> O	H	H	H	CH	H	H	ethoxy	ethoxy	H	none	none

Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent; R<sub>4</sub> and R<sub>13</sub> equal H).

<u>R<sub>gnt.</sub></u> <u>N<sub>o.</sub></u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
125N	CF <sub>3</sub> O	H	H	H	CH	H	H	CH <sub>3</sub> CO <sub>2</sub>	CH <sub>3</sub> CO <sub>2</sub>	H	none	none
126N	CF <sub>3</sub> O	H	H	H	CH	H	H	CH <sub>3</sub> O	CH <sub>3</sub> CO <sub>2</sub>	H	none	none
127N	CF <sub>3</sub> O	H	H	H	CH	H	H	n-butoxy	H	H	none	none
128N	CF <sub>3</sub> O	H	H	H	CH	H	H	CH <sub>3</sub> O	H	H	none	none
129N	CF <sub>3</sub> O	H	H	H	CH	H	H	H	CH <sub>3</sub> O	H	none	none
130N	CH <sub>3</sub> O	H	H	H	CH	H	H	CH <sub>3</sub> O	H	H	none	none
131N	CH <sub>3</sub> O	H	H	H	CH	H	H	H	CF <sub>3</sub> O	H	none	none
132N	CF <sub>3</sub> O	H	H	H	CH	H	H	H	ethoxy	H	none	none
133N	CF <sub>3</sub> O	H	H	H	CH	H	H	H	n-propoxy	H	none	none
134N	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub> O	H	H	H	CH	H	H	CF <sub>3</sub> O	H	H	none	none
135N	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub> O	H	H	H	CH	H	H	C <sub>6</sub> H <sub>5</sub> O	H	H	none	none

Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent; R<sub>4</sub> and R<sub>13</sub> equal H).

<u>R<sub>gnt.</sub></u> <u>No.</u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
136N	ethoxy	H	H	H	CH	H	H	CF <sub>3</sub> O	H	H	none	none
137N	$R_5 + R_6 = OCH_2O$		H	H	CH	H	H	CF <sub>3</sub> O	H	H	none	none
138N	$R_5 + R_6 = OCH_2O$		H	H	CH	H	H	C <sub>6</sub> H <sub>5</sub> O	H	H	none	none
139N	$R_5 + R_6 = OCH_2CH_2O$		H	H	CH	H	H	CF <sub>3</sub> O	H	H	none	none
140N	CH <sub>3</sub> O	CH <sub>3</sub> O	H	H	CH	H	H	CF <sub>3</sub> O	H	H	none	none
141N	$R_5 + R_6 = OCH_2CH_2CH_2O$		H	H	CH	H	H	CF <sub>3</sub> O	H	H	none	none
142N	cyclo pentoxy	CH <sub>3</sub> O	H	H	CH	H	H	CF <sub>3</sub> O	H	H	none	none
143N	H	C <sub>6</sub> H <sub>5</sub> O	H	H	CH	H	H	CF <sub>3</sub> O	H	H	none	none
144N	CH <sub>3</sub> O	CH <sub>3</sub> O	CH <sub>3</sub> O	H	CH	H	H	CF <sub>3</sub> O	H	H	none	none
145N	H	CF <sub>3</sub> O	H	H	CH	H	H	CF <sub>3</sub> O	H	H	none	none
146N	H	Benzyl	H	H	CH	H	H	CF <sub>3</sub> O	H	H	none	none

Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent;R<sub>4</sub> and R<sub>13</sub> equal H).

<u>Rgnt.</u> <u>No.</u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
147N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	R <sub>10</sub> +R <sub>11</sub> =OCH <sub>2</sub> CH <sub>2</sub> O		H	none	none
148N	H	CF <sub>3</sub> O	H	H	CH	H	H	CF <sub>3</sub>	H	H	none	none
149N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	CF <sub>3</sub>	H	H	none	none
150N	C <sub>6</sub> H <sub>5</sub>	H	H	H	CH	H	H	CF <sub>3</sub>	H	H	none	none
151N	H	C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	CF <sub>3</sub>	H	H	none	none
152N	CN	H	H	H	CH	H	H	CF <sub>3</sub>	H	H	none	none
153N	H	OCF <sub>3</sub>	H	H	CH	H	H	CF <sub>3</sub>	H	H	none	none
154N	OCF <sub>3</sub>	H	H	H	CH	H	H	H	CF <sub>3</sub>	H	none	none
155N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	H	CF <sub>3</sub>	H	none	none
156N	C <sub>6</sub> H <sub>5</sub>	H	H	H	CH	H	H	H	CF <sub>3</sub>	H	none	none
157N	H	C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	H	CF <sub>3</sub>	H	none	none

Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent; R<sub>4</sub> and R<sub>13</sub> equal H).

<u>R<sub>gnt.</sub></u> <u>No.</u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
158N	CN	H	H	H	CH	H	H	H	CF <sub>3</sub>	H	none	none
159N	OCF <sub>3</sub>	H	H	H	CH	H	H	H	CF <sub>3</sub>	H	none	none
160N	CF <sub>3</sub>	H	H	H	CH	H	H	H	C <sub>6</sub> H <sub>5</sub>	H	none	none
161N	CF <sub>3</sub>	H	H	H	CH	H	H	3-CF <sub>3</sub> - C <sub>6</sub> H <sub>5</sub> O	H	H	none	none
162N	CF <sub>3</sub>	H	H	H	CH	H	H	C <sub>6</sub> H <sub>5</sub> O	H	H	none	none
163N	CF <sub>3</sub>	H	H	H	CH	H	H	CF <sub>3</sub> O	H	H	none	none
164N	H	CF <sub>3</sub>	H	H	CH	H	H	H	C <sub>6</sub> H <sub>5</sub>	H	none	none
165N	H	CF <sub>3</sub>	H	H	CH	H	H	3-CF <sub>3</sub> - C <sub>6</sub> H <sub>5</sub> O	H	H	none	none
166N	H	CF <sub>3</sub>	H	H	CH	H	H	CF <sub>3</sub> O	H	H	none	none

Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent; R<sub>4</sub> and R<sub>13</sub> equal H).

<u>R<sub>gent</sub></u> <u>No.</u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
167N	H	CF <sub>3</sub>	H	H	CH	H	H	C <sub>6</sub> H <sub>5</sub> O	H	H	none	none
168N	CF <sub>3</sub>	H	CF <sub>3</sub>	H	CH	H	H	CF <sub>3</sub> O	H	H	none	none
169N	CF <sub>3</sub>	H	CF <sub>3</sub>	H	CH	H	H	C <sub>6</sub> H <sub>5</sub> O	H	H	none	none
170N	CF <sub>3</sub> O	H	H	H	CH	H	H	CF <sub>3</sub>	H	CF <sub>3</sub>	none	none
171N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	CF <sub>3</sub>	H	CF <sub>3</sub>	none	none
172N	H	C <sub>6</sub> H <sub>5</sub> O	H	H	CH	H	H	C <sub>6</sub> H <sub>5</sub> O	H	H	none	none
173N	H	CF <sub>3</sub> O	H	H	CH	H	H	CF <sub>3</sub> O	H	H	none	none
174N	H	CF <sub>3</sub> O	H	H	CH	H	H	H	C <sub>6</sub> H <sub>5</sub> O	H	none	none
175N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	H	C <sub>6</sub> H <sub>5</sub> O	H	none	none
176N	H	C <sub>6</sub> H <sub>5</sub> O	H	H	CH	H	H	H	OCF <sub>3</sub>	H	none	none
177N	H	C <sub>6</sub> H <sub>5</sub> O	H	H	CH	H	H	H	C <sub>6</sub> H <sub>5</sub> O	H	none	none

Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent; R<sub>4</sub> and R<sub>13</sub> equal H).

<u>R<sub>gent</sub></u> <u>No.</u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
178N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	H	CN	H	none	none
179N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	CN	H	H	none	none
180N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	NO <sub>2</sub>	H	H	none	none
181N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	H	NO <sub>2</sub>	H	none	none
182N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	H	SO <sub>2</sub> CH <sub>3</sub>	H	none	none
183N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	H	2-NO <sub>2</sub> -4- Cl-C <sub>6</sub> H <sub>3</sub> O	H	none	none
184N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	4-Cl-C <sub>6</sub> H <sub>4</sub> O	H	H	none	none
185N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	3,4-Cl-C <sub>6</sub> H <sub>3</sub> O	H	H	none	none
186N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	3-CF <sub>3</sub> - C <sub>6</sub> H <sub>3</sub> O	H	H	none	none

Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent; R<sub>4</sub> and R<sub>13</sub> equal H).

<u>R<sub>gnt.</sub></u> <u>N<sub>o.</sub></u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
187N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	3,5-Cl-C <sub>6</sub> H <sub>3</sub> O	H	H	none	none
188N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	H	CH <sub>3</sub> O	H	none	none
189N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	H	CO <sub>2</sub> CH <sub>3</sub>	H	none	none
190N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	3-CH <sub>3</sub> O C <sub>6</sub> H <sub>5</sub> O	H	H	none	none
191N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	4-CH <sub>3</sub> O C <sub>6</sub> H <sub>5</sub> O	H	H	none	none
193N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	CO <sub>2</sub> CH <sub>3</sub>	H	H	none	none
194N	CN	H	H	H	CH	H	H	OCF <sub>3</sub>	H	H	none	none
195N	NO <sub>2</sub>	H	H	H	CH	H	H	OCF <sub>3</sub>	H	H	none	none
196N	H	CN	H	H	CH	H	H	OCF <sub>3</sub>	H	H	none	none



Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent; R<sub>4</sub> and R<sub>13</sub> equal H).

<u>Rgnt.</u> <u>No.</u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
197N	H	NO <sub>2</sub>	H	H	CH	H	H	OCF <sub>3</sub>	H	H	none	none
198N	SO <sub>2</sub> CH <sub>3</sub>	H	H	H	CH	H	H	OCF <sub>3</sub>	H	H	none	none
199N	H	SO <sub>2</sub> CH <sub>3</sub>	H	H	CH	H	H	OCF <sub>3</sub>	H	H	none	none
200N	H	4-F-C <sub>6</sub> H <sub>5</sub> SO <sub>2</sub>	H	H	CH	H	H	OCF <sub>3</sub>	H	H	none	none
201N	SO <sub>2</sub> N (CH <sub>3</sub> ) <sub>2</sub>	H	H	H	CH	H	H	OCF <sub>3</sub>	H	H	none	none
202N	H	SO <sub>2</sub> N (CH <sub>3</sub> ) <sub>2</sub>	H	H	CH	H	H	OCF <sub>3</sub>	H	H	none	none
203N	H	CONH <sub>2</sub>	H	H	CH	H	H	OCF <sub>3</sub>	H	H	none	none
204N	H	CONH-	H	H	CH	H	H	OCF <sub>3</sub>	H	H	none	none

Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent; R<sub>4</sub> and R<sub>13</sub> equal H).

<u>R<sub>gnt.</sub></u> <u>No.</u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
205N	H	CO <sub>2</sub> CH <sub>3</sub>	H	H	CH	H	H	OCF <sub>3</sub>	H	H	none	none
206N	H	CO <sub>2</sub> C <sub>4</sub> H <sub>9</sub>	H	H	CH	H	H	OCF <sub>3</sub>	H	H	none	none
207N	H	4-Cl-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	C <sub>6</sub> H <sub>5</sub> O	H	H	none	none
208N	H	4-CF <sub>3</sub> O-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	CF <sub>3</sub> O	H	H	none	none
209N	4-F-C <sub>6</sub> H <sub>4</sub> O	H	H	H	CH	H	H	CF <sub>3</sub> O	H	H	none	none
210N	C <sub>6</sub> F <sub>5</sub> O	H	H	H	CH	H	H	CF <sub>3</sub> O	H	H	none	none
211N	H	4-F-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	CF <sub>3</sub> O	H	H	none	none
212N	H	4-CN-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	CF <sub>3</sub> O	H	H	none	none
213N	H	4-C <sub>6</sub> H <sub>5</sub> -C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	CF <sub>3</sub> O	H	H	none	none

Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent; R<sub>4</sub> and R<sub>13</sub> equal H).

<u>R<sub>gnt.</sub></u> <u>No.</u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
214N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	CH <sub>3</sub>	H	CF <sub>3</sub> O	H	H	none	none
215N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	CH <sub>3</sub>	H	NO <sub>2</sub>	H	H	none	none
216N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	CH <sub>3</sub>	H	H	CN	H	none	none
217N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	3- CF <sub>3</sub> C <sub>6</sub> H 5	H	CF <sub>3</sub>	H	H	none	none
218N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	C <sub>6</sub> H 5	H	H	C <sub>6</sub> H <sub>5</sub>	H	none	none
219N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	C <sub>6</sub> H 5	H	CF <sub>3</sub>	H	H	none	none
220N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	CH <sub>3</sub>	H	F	H	H	none	none

Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent; R<sub>4</sub> and R<sub>13</sub> equal H).

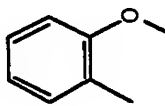
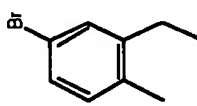
<u>Rgnt.</u> <u>No.</u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
221N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	CF <sub>3</sub>	H	H	H	H	none	none
222N	bond to -O- of R <sub>6</sub> aryl group		H	H	CH	H	H	CF <sub>3</sub> O	H	H	none	none
223N	to CH <sub>2</sub> of R <sub>6</sub> aryl group		H	H	CH	H	H	CF <sub>3</sub> O	H	H	none	none
224N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	H	H	none	none
225N	4-Cl-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	H	H	none	none
226N	4-F-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	H	H	none	none

Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent; R<sub>4</sub> and R<sub>13</sub> equal H).

<u>R<sub>gnt.</sub></u> <u>N<sub>o.</sub></u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
227N	3,4-Cl- C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	H	H	none	none
228N	H	C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	H	H	none	none
229N	H	4-Cl-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	H	H	none	none
230N	H	4-F-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	H	H	none	none
231N	H	4-Br-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	H	H	none	none
232N	4-Br-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	H	H	none	none
233N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>3</sub>	H	H	none	none
234N	4-Cl-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>3</sub>	H	H	none	none
235N	4-F-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>3</sub>	H	H	none	none
236N	3,4-Cl- C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>3</sub>	H	H	none	none

Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent; R<sub>4</sub> and R<sub>13</sub> equal H).

<u>Rgnt.</u> <u>No.</u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
237N	H	C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>3</sub>	H	H	none	none
238N	H	4-Cl-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>3</sub>	H	H	none	none
239N	H	4-F-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>3</sub>	H	H	none	none
240N	H	4-Br-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>3</sub>	H	H	none	none
241N	4-Br-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>3</sub>	H	H	none	none
242N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>3</sub>	H	H	none	none
243N	4-Cl-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCCl <sub>2</sub> CCl <sub>2</sub> H	H	H	none	none
244N	4-F-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCCl <sub>2</sub> CCl <sub>2</sub> H	H	H	none	none
245N	3,4-Cl-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCCl <sub>2</sub> CCl <sub>2</sub> H	H	H	none	none
246N	H	C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCCl <sub>2</sub> CCl <sub>2</sub> H	H	H	none	none
247N	H	4-Cl-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCCl <sub>2</sub> CCl <sub>2</sub> H	H	H	none	none

Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent; R<sub>4</sub> and R<sub>13</sub> equal H).

<u>R<sub>gnt.</sub></u> <u>N<sub>o.</sub></u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
248N	H	4-F-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCCl <sub>2</sub> CCl <sub>2</sub> H	H	H	none	none
249N	H	4-Br-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCCl <sub>2</sub> CCl <sub>2</sub> H	H	H	none	none
250N	4-Br-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCCl <sub>2</sub> CCl <sub>2</sub> H	H	H	none	none
251N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCCl <sub>2</sub> CCl <sub>3</sub>	H	H	none	none
252N	4-Cl-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCCl <sub>2</sub> CCl <sub>3</sub>	H	H	none	none
253N	4-F-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCCl <sub>2</sub> CCl <sub>3</sub>	H	H	none	none
254N	3,4-Cl-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCCl <sub>2</sub> CCl <sub>3</sub>	H	H	none	none
255N	H	C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCCl <sub>2</sub> CCl <sub>3</sub>	H	H	none	none
256N	H	4-Cl-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCCl <sub>2</sub> CCl <sub>3</sub>	H	H	none	none
257N	H	4-F-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCCl <sub>2</sub> CCl <sub>3</sub>	H	H	none	none
258N	H	4-Br-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCCl <sub>2</sub> CCl <sub>3</sub>	H	H	none	none

Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent; R<sub>4</sub> and R<sub>13</sub> equal H).

<u>R<sub>gnt.</sub></u> <u>No.</u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
259N	4-Br-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCCl <sub>2</sub> CCl <sub>3</sub>	H	H	none
260N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCCl <sub>2</sub> CF <sub>3</sub>	H	H	none
261N	4-Cl-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCCl <sub>2</sub> CF <sub>3</sub>	H	H	none
262N	4-F-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCCl <sub>2</sub> CF <sub>3</sub>	H	H	none
263N	3,4-Cl-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCCl <sub>2</sub> CF <sub>3</sub>	H	H	none
264N	H	C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCCl <sub>2</sub> CF <sub>3</sub>	H	H	none
265N	H	4-Cl-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCCl <sub>2</sub> CF <sub>3</sub>	H	H	none
266N	H	4-F-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCCl <sub>2</sub> CF <sub>3</sub>	H	H	none
267N	H	4-Br-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCCl <sub>2</sub> CF <sub>3</sub>	H	H	none
268N	4-Br-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCCl <sub>2</sub> CF <sub>3</sub>	H	H	none
269N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> CCl <sub>3</sub>	H	H	none



Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent; R<sub>4</sub> and R<sub>13</sub> equal H).

<u>R<sub>gnt.</sub></u> <u>No.</u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
270N	4-Cl-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> CCl <sub>3</sub>	H	H	none
271N	4-F-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> CCl <sub>3</sub>	H	H	none
272N	3,4-Cl-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> CCl <sub>3</sub>	H	H	none
273N	H	C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>2</sub> CCl <sub>3</sub>	H	H	none
274N	H	4-Cl-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>2</sub> CCl <sub>3</sub>	H	H	none
275N	H	4-F-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>2</sub> CCl <sub>3</sub>	H	H	none
276N	H	4-Br-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>2</sub> CCl <sub>3</sub>	H	H	none
277N	4-Br-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> CCl <sub>3</sub>	H	H	none
278N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	OCF <sub>2</sub> CF <sub>2</sub> H	H	none
279N	4-Cl-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	OCF <sub>2</sub> CF <sub>2</sub> H	H	none
280N	4-F-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	OCF <sub>2</sub> CF <sub>2</sub> H	H	none

Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent; R<sub>4</sub> and R<sub>13</sub> equal H).

<u>R<sub>gent</sub></u> <u>No.</u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
281N	3,4-Cl- C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	OCF <sub>2</sub> CF <sub>2</sub> H	H	none	none
282N	H	C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	OCF <sub>2</sub> CF <sub>2</sub> H	H	none	none
283N	H	4-Cl-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	OCF <sub>2</sub> CF <sub>2</sub> H	H	none	none
284N	H	4-F-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	OCF <sub>2</sub> CF <sub>2</sub> H	H	none	none
285N	H	4-Br-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	OCF <sub>2</sub> CF <sub>2</sub> H	H	none	none
286N	4-Br-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	OCF <sub>2</sub> CF <sub>2</sub> H	H	none	none
287N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>3</sub>	OCF <sub>3</sub>	H	none	none
288N	4-Cl-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>3</sub>	OCF <sub>3</sub>	H	none	none
289N	4-F-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>3</sub>	OCF <sub>3</sub>	H	none	none
290N	3,4-Cl- C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>3</sub>	OCF <sub>3</sub>	H	none	none

Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent; R<sub>4</sub> and R<sub>13</sub> equal H).

<u>R<sub>gnt.</sub></u> <u>N<sub>o.</sub></u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
291N	H	C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>3</sub>	OCF <sub>3</sub>	H	none	none
292N	H	4-Cl-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>3</sub>	OCF <sub>3</sub>	H	none	none
293N	H	4-F-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>3</sub>	OCF <sub>3</sub>	H	none	none
294N	H	4-Br-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>3</sub>	OCF <sub>3</sub>	H	none	none
295N	4-Br-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>3</sub>	OCF <sub>3</sub>	H	none	none
296N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> H	OCF <sub>2</sub> H	H	none	none
297N	4-Cl-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> H	OCF <sub>2</sub> H	H	none	none
298N	4-F-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> H	OCF <sub>2</sub> H	H	none	none
299N	3,4-Cl-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> H	OCF <sub>2</sub> H	H	none	none
300N	H	C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>2</sub> H	OCF <sub>2</sub> H	H	none	none
301N	H	4-Cl-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>2</sub> H	OCF <sub>2</sub> H	H	none	none

Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent; R<sub>4</sub> and R<sub>13</sub> equal H).

<u>R<sub>gnt.</sub></u> <u>No.</u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
302N	H	4-F-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>2</sub> H	OCF <sub>2</sub> H	H	none	none
303N	H	4-Br-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	OCF <sub>2</sub> H	OCF <sub>2</sub> H	H	none	none
304N	4-Br-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	OCF <sub>2</sub> H	OCF <sub>2</sub> H	H	none	none
305N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	R <sub>10</sub> +R <sub>11</sub> =OCF <sub>2</sub> CF <sub>2</sub> O		H	none	none
306N	4-Cl-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	R <sub>10</sub> +R <sub>11</sub> =OCF <sub>2</sub> CF <sub>2</sub> O		H	none	none
307N	4-F-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	R <sub>10</sub> +R <sub>11</sub> =OCF <sub>2</sub> CF <sub>2</sub> O		H	none	none
308N	3,4-Cl-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	R <sub>10</sub> +R <sub>11</sub> =OCF <sub>2</sub> CF <sub>2</sub> O		H	none	none
309N	H	C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	R <sub>10</sub> +R <sub>11</sub> =OCF <sub>2</sub> CF <sub>2</sub> O		H	none	none
310N	H	4-Cl-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	R <sub>10</sub> +R <sub>11</sub> =OCF <sub>2</sub> CF <sub>2</sub> O		H	none	none
311N	H	4-F-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	R <sub>10</sub> +R <sub>11</sub> =OCF <sub>2</sub> CF <sub>2</sub> O		H	none	none
312N	H	4-Br-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	R <sub>10</sub> +R <sub>11</sub> =OCF <sub>2</sub> CF <sub>2</sub> O		H	none	none

Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent; R<sub>4</sub> and R<sub>13</sub> equal H).

<u>R<sub>gnt.</sub></u> <u>No.</u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
313N	4-Br-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	R <sub>10</sub> +R <sub>11</sub> =OCF <sub>2</sub> CF <sub>2</sub> O		H	none	none
314N	C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	R <sub>10</sub> +R <sub>11</sub> =OCCl <sub>2</sub> CCl <sub>2</sub> O		H	none	none
315N	4-Cl-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	R <sub>10</sub> +R <sub>11</sub> =OCCl <sub>2</sub> CCl <sub>2</sub> O		H	none	none
316N	4-F-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	R <sub>10</sub> +R <sub>11</sub> =OCCl <sub>2</sub> CCl <sub>2</sub> O		H	none	none
317N	3,4-Cl-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	R <sub>10</sub> +R <sub>11</sub> =OCCl <sub>2</sub> CCl <sub>2</sub> O		H	none	none
318N	H	C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	R <sub>10</sub> +R <sub>11</sub> =OCCl <sub>2</sub> CCl <sub>2</sub> O		H	none	none
319N	H	4-Cl-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	R <sub>10</sub> +R <sub>11</sub> =OCCl <sub>2</sub> CCl <sub>2</sub> O		H	none	none
320N	H	4-F-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	R <sub>10</sub> +R <sub>11</sub> =OCCl <sub>2</sub> CCl <sub>2</sub> O		H	none	none
321N	H	4-Br-C <sub>6</sub> H <sub>5</sub>	H	H	CH	H	H	R <sub>10</sub> +R <sub>11</sub> =OCCl <sub>2</sub> CCl <sub>2</sub> O		H	none	none
322N	4-Br-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	R <sub>10</sub> +R <sub>11</sub> =OCCl <sub>2</sub> CCl <sub>2</sub> O		H	none	none
323N	H	H	H	H	CH	H	H	OH	H	H	none	none

Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent;R<sub>4</sub> and R<sub>13</sub> equal H).

<u>R<sub>gnt.</sub></u> <u>N<sub>o.</sub></u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
324N	H	H	H	H	CH	H	H	OH	OH	H	none	none
325N	H	H	H	H	CH	H	H	H	OH	H	none	none
326N	H	H	H	H	CH	H	H	OCH <sub>2</sub> CF <sub>3</sub>	H	H	none	none
327N	H	H	H	H	CH	H	H	H	OCH <sub>2</sub> CF <sub>3</sub>	H	none	none
328N	H	H	H	H	CH	H	H	OCH <sub>2</sub> CF <sub>2</sub> CF <sub>3</sub>	H	H	none	none
329N	H	H	H	H	CH	H	H	OCH <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>	H	H	none	none
330N	H	H	H	H	CH	H	H	OCH(CF <sub>3</sub> ) <sub>3</sub>	H	H	none	none
331N	H	4-F-C <sub>6</sub> H <sub>5</sub> O	H	H	CH	H	H	H	H	H	none	none
332N	4-F-C <sub>6</sub> H <sub>5</sub> O	H	H	H	CH	H	H	H	H	H	none	none
333N	H	cyclo-hexoxy	H	H	CH	H	H	H	H	H	none	none
334N	cyclo-hexoxy	H	H	H	CH	H	H	H	H	H	none	none
335N	H	C(CH <sub>3</sub> ) <sub>3</sub>	H	H	CH	H	H	H	H	H	none	none

Table 4. (continued) Structure of "Secondary Phenyl Amine" Reagents (Z is covalent bond; there is no R<sub>15</sub> substituent; R<sub>4</sub> and R<sub>13</sub> equal H).

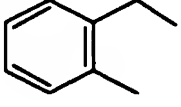
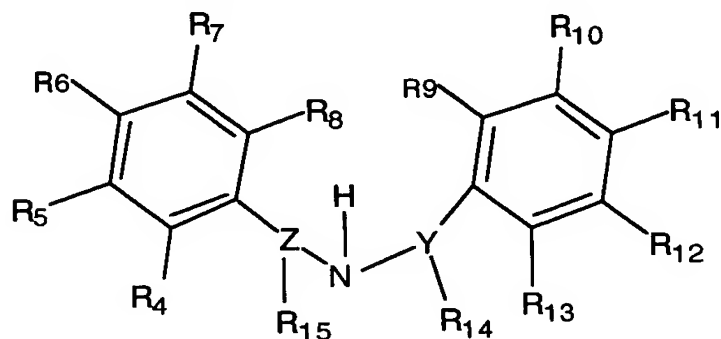
<u>R<sub>gnt.</sub></u> <u>No.</u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>8</sub></u>	<u>Y</u>	<u>R<sub>14</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>Spacer</u>	<u>Spacer</u> <u>Bond</u> <u>Points</u>
336N	F	H	H	H	CH	H	H		bond to indicated phenyl carbon of R <sub>10</sub> subst.	H	none	none

Table 5. Structure of "Secondary Phenyl Amine" Reagents (Y and Z each equal CH; R<sub>7</sub>, R<sub>8</sub>, R<sub>12</sub>, R<sub>13</sub>, R<sub>14</sub>, and R<sub>15</sub> each equal H).



Secondary  
Phenyl Amine  
(XIII-A)

Reagent Number	R <sub>4</sub>	R <sub>5</sub>	R <sub>6</sub>	R <sub>9</sub>	R <sub>10</sub>	R <sub>11</sub>
1DB	H	OCF <sub>3</sub>	H	H	OCF <sub>3</sub>	H
2DB	H	Cl	H	H	H	CF <sub>3</sub>
3DB	H	Br	H	H	OCF <sub>3</sub>	H
4DB	H	Cl	H	H	OCF <sub>3</sub>	H
5DB	H	Cl	H	H	CF <sub>3</sub>	H
6DB	H	H	Cl	H	CF <sub>3</sub>	H
7DB	H	F	H	H	OCF <sub>3</sub>	H
8DB	H	H	Cl	H	H	CF <sub>3</sub>
9DB	H	F	H	H	H	CF <sub>3</sub>
10DB	H	H	F	H	H	CF <sub>3</sub>
11DB	F	H	H	H	H	CF <sub>3</sub>
12DB	H	Cl	H	CF <sub>3</sub>	H	H
13DB	H	H	Cl	CF <sub>3</sub>	H	H
14DB	Cl	H	H	CF <sub>3</sub>	H	H
15DB	H	F	H	CH <sub>3</sub>	H	H
16DB	H	H	F	H	H	CH <sub>3</sub>
17DB	H	F	H	H	CH <sub>3</sub>	H
18DB	F	H	H	CH <sub>3</sub>	H	H



Table 5. (continued) Structure of "Secondary Phenyl Amine" Reagents  
(Y and Z each equal CH; R<sub>7</sub>, R<sub>8</sub>, R<sub>12</sub>, R<sub>13</sub>, R<sub>14</sub>, and R<sub>15</sub> each equal H).

<u>Reagent Number</u>	<u>R<sub>4</sub></u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>
19DB	H	H	F	H	CH <sub>3</sub>	H
20DB	F	H	H	H	H	CH <sub>3</sub>
21DB	F	H	H	H	CF <sub>3</sub>	H
22DB	Cl	H	H	H	CF <sub>3</sub>	H
23DB	H	F	H	CF <sub>3</sub>	H	H
24DB	H	H	F	CF <sub>3</sub>	H	H
25DB	H	F	H	H	CF <sub>3</sub>	H
26DB	H	H	F	H	CF <sub>3</sub>	H
27DB	H	OCF <sub>3</sub>	H	H	H	OCF <sub>3</sub>

As summarized in the general Scheme 1 and specific descriptions above, Schemes 3, 4, 9, and 10 illustrate the principles of Scheme 1 for the preparation of specifically substituted "Secondary Heteroaryl Amines" (XIIIA-H) having 0 to 2 aryl groups and 0 to 2 aromatic heterocyclyl groups and

5 "Secondary Phenyl Amines" (XIII-A) having two aryl groups.

Synthetic Scheme 2 shows the preparation of the class of compounds of the present invention corresponding to Formula I-H ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-alkanols"), Formula I-HP ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral

10 Halogenated 1-Substitutedamino-2-propanols"), Formula I-HPC ("Polycyclic Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols"), Formula I-C ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols"), and Formula I-CP ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") wherein A and Q are

15 independently aryl and heteroaryl.

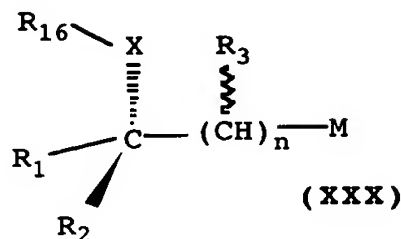
Derivatives of "Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-alkanols", "Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-propanols", "Polycyclic Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols", "Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols", and "Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols", wherein A and Q are independently aryl and heteroaryl, in which the hetero atom (-O-) is attached to an alkyl group removed from the amine by three or more carbons are readily prepared by

20 anion chemistry using Method B of Scheme 2. The anion of "Generic Secondary Amine" amines, hydroxylamines, and hydrazines of Formula XIII are readily formed by dissolving the specific amine, hydroxylamine, or hydrazine in an aprotic solvent, such as tetrahydrofuran, toluene, ether, dimethylformamide, and dimethylformamide, under anhydrous conditions. The

25 solution is cooled to a temperature between -78 and 0°C, preferably between -78 and -60°C and the anion formed by the addition of at least one equivalent of a strong, aprotic, non-nucleophilic base such as NaH or n-butyllithium under an inert atmosphere for each acidic group present. Maintaining the temperature between -78 and 0°C, preferably between -78 and -60°C, with suitable

30 cooling, an appropriate alkyl halide, alkyl benzenesulfonate such as a alkyl

tosylate, alkyl mesylate, alkyl triflate or similar alkylating reagent of the general structure:



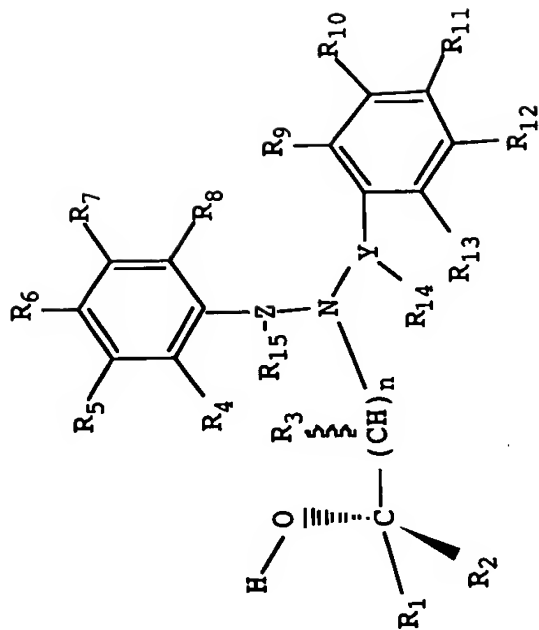
- where M is a readily displaceable group such as chloride, bromide, iodide, tosylate, triflate, and mesylate, X is oxy, and XXX is a chiral reagent in the indicated (R)-configuration. After allowing the reaction mixture to warm to room temperature, the reaction product is added to water, neutralized if necessary, and extracted with a water-immiscible solvent such as diethyl ether or methylene chloride. The combined aprotic solvent extract is washed with saturated brine, dried over drying agent such as anhydrous MgSO<sub>4</sub> and concentrated *in vacuo* to yield crude Formula I-H ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-alkanols"), Formula I-HP ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-propanols"), Formula I-HPC ("Polycyclic Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols"), Formula I-C ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols"), and Formula I-CP ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols"), wherein A and Q are independently aryl and heteroaryl. This material is purified, for example, by eluting through silica gel with 5-40% of a medium polar solvent such as ethyl acetate in a non-polar solvent such as hexanes to yield Formula I-H ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-alkanols"), Formula I-HP ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-propanols"), Formula I-HPC ("Polycyclic Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols"), Formula I-C ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols"), and Formula I-CP ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols"). Products are tested for purity by HPLC. If necessary, Formula I-H ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-alkanols"), Formula I-HP ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral

Halogenated 1-Substitutedamino-2-propanols”), Formula I-HPC (“Polycyclic Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”), Formula I-C (“Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols”), and Formula I-CP (“Polycyclic Phenyl (R)-Chiral

- 5 Halogenated 1-Substitutedamino-2-Propanols”) compounds are purified by additional chromatography or recrystallization. Products are structurally confirmed by low and high resolution mass spectrometry and NMR. Examples of specific compounds prepared are summarized in Tables 6 and 7.

- Compounds of Formula (XXX), which can be used to prepare the
- 10 “Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanol” compounds of Tables 6 and 7, are given in Table 2. Reagents 1a and 2a in Table 2 are prepared from the corresponding alcohols. (R)-Chiral alcohol precursors to 1a, 2a, and similiar alcohols that can be envisioned by one of inventive skill can be obtained from the corresponding racemic mixture of the
- 15 R-enatiomer and S-enantiomer by separation procedures using preparative gas chromatography and high pressure liquid chromatography using chiral chromatographic columns. The tosylates of chiral alcohols and racemic mixtures are readily obtained by reacting the corresponding alcohol with tosyl chloride using procedures found in House’s Modern Synthetic Reactions,
- 20 Chapter 7, W. A. Benjamin, Inc., Shriner, Fuson, and Curtin in The Systematic Indentification of Organic Compounds, 5th Edition, John Wiley & Sons, and Fieser and Fieser in Reagents for Organic Synthesis, Volume 1, John Wiley & Sons, which are incorporated herein by reference.

Table 6. Structure of Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols  
(Y is CH; R<sub>8</sub>, R<sub>9</sub>, R<sub>12</sub>, R<sub>13</sub>, and R<sub>14</sub> are each H; Z is covalent bond and R<sub>15</sub> is absent).



Inhibitor Number Column 1 + Column 2		R <sub>1</sub>	n	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	R <sub>6</sub>	R <sub>7</sub>	R <sub>10</sub>	R <sub>11</sub>
Reagent	Reagent										
1A	1N	CF <sub>3</sub>	3	H	H	H	C <sub>6</sub> H <sub>5</sub> O	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	H
1A	2N	CF <sub>3</sub>	3	H	H	H	OCF <sub>3</sub>	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	H

Table 6. (continued) Structure of Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols  
(Y is CH; R<sub>8</sub>, R<sub>9</sub>, R<sub>12</sub>, R<sub>13</sub>, and R<sub>14</sub> are each H; Z is covalent bond and R<sub>15</sub> is absent).

Inhibitor Number Column 1+Column 2		R <sub>1</sub>	n	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	R <sub>6</sub>	R <sub>7</sub>	R <sub>10</sub>	R <sub>11</sub>
Reagent	Reagent										
1A	3N	CF <sub>3</sub>	3	H	H	F	H	H	F	OCF <sub>2</sub> CF <sub>2</sub> H	H
1A	4N	CF <sub>3</sub>	3	H	H	H	F	H	H	OCF <sub>2</sub> CF <sub>2</sub> H	H
1A	5N	CF <sub>3</sub>	3	H	H	H	C <sub>6</sub> H <sub>5</sub> O	H	H	OCF <sub>3</sub>	H
1A	6N	CF <sub>3</sub>	3	H	H	H	OCF <sub>3</sub>	H	H	OCF <sub>3</sub>	H
1A	7N	CF <sub>3</sub>	3	H	H	H	H	phenyl	H	OCF <sub>3</sub>	H
1A	8N	CF <sub>3</sub>	3	H	H	H	phenyl	H	H	OCF <sub>3</sub>	H
1A	9N	CF <sub>3</sub>	3	H	H	H	H	H	H	OCF <sub>3</sub>	H
1A	10N	CF <sub>3</sub>	3	H	H	H	Br	H	H	OCF <sub>3</sub>	H
1A	11N	CF <sub>3</sub>	3	H	H	H	CF <sub>3</sub>	F	H	CF <sub>3</sub>	H
1A	12N	CF <sub>3</sub>	3	H	H	H	CH <sub>3</sub>	H	H	CF <sub>3</sub>	H
1A	13N	CF <sub>3</sub>	3	H	H	H	CF <sub>3</sub>	H	H	CF <sub>3</sub>	H
1A	14N	CF <sub>3</sub>	3	H	H	H	CH <sub>3</sub>	H	H	OCF <sub>3</sub>	H

Inhibitor Number Column1+Column 2		R <sub>1</sub>	n	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	R <sub>6</sub>	R <sub>7</sub>	R <sub>10</sub>	R <sub>11</sub>
Reagent	Reagent										
1A	15N	CF <sub>3</sub>	3	H	H	H	F	F	H	OCF <sub>3</sub>	H
1A	16N	CF <sub>3</sub>	3	H	H	H	Br	H	H	CF <sub>3</sub>	H
1A	17N	CF <sub>3</sub>	3	H	H	H	CF <sub>3</sub>	F	H	OCF <sub>3</sub>	H
1A	18N	CF <sub>3</sub>	3	H	H	H	F	H	H	OCF <sub>3</sub>	H
1A	19N	CF <sub>3</sub>	3	H	H	H	Cl	H	H	OCF <sub>3</sub>	H
1A	20N	CF <sub>3</sub>	3	H	H	H	F	H	H	CF <sub>3</sub>	H
1A	21N	CF <sub>3</sub>	3	H	H	H	F	F	H	CF <sub>3</sub>	H
1A	22N	CF <sub>3</sub>	3	H	H	H	Cl	H	H	CF <sub>3</sub>	H
1A	23N	CF <sub>3</sub>	3	H	H	H	F	H	H	phenoxy	H
1A	24N	CF <sub>3</sub>	3	H	H	H	CF <sub>3</sub>	Cl	H	CH <sub>3</sub>	H
1A	25N	CF <sub>3</sub>	3	H	H	H	CF <sub>3</sub>	F	H	CH <sub>3</sub>	H
1A	26N	CF <sub>3</sub>	3	H	H	H	H	H	H	CF <sub>3</sub>	H

Inhibitor Number Column1+Column 2		R <sub>1</sub>	n	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	R <sub>6</sub>	R <sub>7</sub>	R <sub>10</sub>	R <sub>11</sub>
Reagent	Reagent										
1A	15N	CF <sub>3</sub>	3	H	H	H	F	F	H	OCF <sub>3</sub>	H
1A	16N	CF <sub>3</sub>	3	H	H	H	Br	H	H	CF <sub>3</sub>	H
1A	17N	CF <sub>3</sub>	3	H	H	H	CF <sub>3</sub>	F	H	OCF <sub>3</sub>	H
1A	18N	CF <sub>3</sub>	3	H	H	H	F	H	H	OCF <sub>3</sub>	H
1A	19N	CF <sub>3</sub>	3	H	H	H	Cl	H	H	OCF <sub>3</sub>	H
1A	20N	CF <sub>3</sub>	3	H	H	H	F	H	H	CF <sub>3</sub>	H
1A	21N	CF <sub>3</sub>	3	H	H	H	F	F	H	CF <sub>3</sub>	H
1A	22N	CF <sub>3</sub>	3	H	H	H	Cl	H	H	CF <sub>3</sub>	H
1A	23N	CF <sub>3</sub>	3	H	H	H	F	H	H	phenoxy	H
1A	24N	CF <sub>3</sub>	3	H	H	H	CF <sub>3</sub>	Cl	H	CH <sub>3</sub>	H
1A	25N	CF <sub>3</sub>	3	H	H	H	CF <sub>3</sub>	F	H	CH <sub>3</sub>	H
1A	26N	CF <sub>3</sub>	3	H	H	H	H	H	H	CF <sub>3</sub>	H

Table 6. (continued) Structure of Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols  
(Y is CH; R<sub>8</sub>, R<sub>9</sub>, R<sub>12</sub>, R<sub>13</sub>, and R<sub>14</sub> are each H; Z is covalent bond and R<sub>15</sub> is absent).

<u>Inhibitor Number</u> <u>Column 1+Column 2</u>		<u>R<sub>1</sub></u>	<u>n</u>	<u>R<sub>2</sub></u>	<u>R<sub>3</sub></u>	<u>R<sub>4</sub></u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>
Reagent	Reagent										
1A	27N	CF <sub>3</sub>	3	H	H	F	F	H	H	CF <sub>3</sub>	H
1A	28N	CF <sub>3</sub>	3	H	H	H	H	OCH <sub>3</sub>	H	CF <sub>3</sub>	H
1A	29N	CF <sub>3</sub>	3	H	H	H	F	F	H	CH <sub>3</sub>	H
1A	30N	CF <sub>3</sub>	3	H	H	H	OCH <sub>3</sub>	H	H	CH <sub>3</sub>	H
1A	31N	CF <sub>3</sub>	3	H	H	H	H	CH <sub>3</sub>	H	H	H
1A	32N	CF <sub>3</sub>	3	H	H	H	Cl	H	H	H	H
1A	33N	CF <sub>3</sub>	3	H	H	H	F	H	H	F	H
1A	34N	CF <sub>3</sub>	3	H	H	H	H	OCH <sub>3</sub>	H	CH <sub>3</sub>	H
1A	35N	CF <sub>3</sub>	3	H	H	H	H	H	H	H	H
1A	36N	CF <sub>3</sub>	3	H	H	H	H	CH <sub>3</sub>	H	CH <sub>3</sub>	H
1A	37N	CF <sub>3</sub>	3	H	H	H	H	Cl	H	H	H
1A	38N	CF <sub>3</sub>	3	H	H	H	F	H	H	3-CF <sub>3</sub> -	H



Table 6. (continued) Structure of Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols  
(Y is CH; R<sub>8</sub>, R<sub>9</sub>, R<sub>12</sub>, R<sub>13</sub>, and R<sub>14</sub> are each H; Z is covalent bond and R<sub>15</sub> is absent).

Inhibitor Number Column1+Column 2		<u>R<sub>1</sub></u>	<u>R<sub>2</sub></u>	<u>R<sub>3</sub></u>	<u>R<sub>4</sub></u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>
Reagent	Reagent									
1A	39N	CF <sub>3</sub>	H	H	H	F	H	H	phenoxy 4-CH <sub>3</sub> O- phenoxy	H
1A	40N	CF <sub>3</sub>	H	H	H	F	H	H	4-Cl- phenoxy	H
1A	41N	CF <sub>3</sub>	H	H	H	F	H	H	H	H
1A	42N	CF <sub>3</sub>	H	H	H	F	H	H	CH <sub>3</sub>	H
1A	43N	CF <sub>3</sub>	H	H	H	F	H	F	CH <sub>3</sub>	H
1A	44N	CF <sub>3</sub>	H	H	F	F	H	H	CH <sub>3</sub>	H
1A	45N	CF <sub>3</sub>	H	H	H	Cl	H	H	CH <sub>3</sub>	H
1A	46N	CF <sub>3</sub>	H	H	H	CH <sub>3</sub>	H	H	CH <sub>3</sub>	H
1A	48N	CF <sub>3</sub>	H	H	H	H	CH <sub>3</sub>	H	CF <sub>3</sub>	H
1A	51N	CF <sub>3</sub>	H	H	H	H	CH <sub>3</sub>	H	F	H

Table 6. (continued) Structure of Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols  
(Y is CH; R<sub>8</sub>, R<sub>9</sub>, R<sub>12</sub>, R<sub>13</sub>, and R<sub>14</sub> are each H; Z is covalent bond and R<sub>15</sub> is absent).

<u>Inhibitor Number</u> <u>Column1+Column 2</u>		<u>R<sub>1</sub></u>	<u>n</u>	<u>R<sub>2</sub></u>	<u>R<sub>3</sub></u>	<u>R<sub>4</sub></u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>
Reagent	Reagent										
1A	52N	CF <sub>3</sub>	3	H	H	H	CF <sub>3</sub>	H	H	F	H
1A	53N	CF <sub>3</sub>	3	H	H	H	CF <sub>3</sub>	H	H	CH <sub>3</sub>	H
1A	54N	CF <sub>3</sub>	3	H	H	H	OCH <sub>3</sub>	H	H	CF <sub>3</sub>	H
1A	56N	CF <sub>3</sub>	3	H	H	H	H	CH <sub>3</sub>	H	CF <sub>3</sub>	H
1A	57N	CF <sub>3</sub>	3	H	H	H	C <sub>6</sub> H <sub>5</sub> O	H	H	H	OCF <sub>3</sub>
1A	58N	CF <sub>3</sub>	3	H	H	H	H	H	H	H	OCF <sub>3</sub>
1A	59N	CF <sub>3</sub>	3	H	H	H	OCF <sub>3</sub>	H	H	H	OCF <sub>3</sub>
1A	60N	CF <sub>3</sub>	3	H	H	H	CF <sub>3</sub>	F	H	H	CF <sub>3</sub>
1A	61N	CF <sub>3</sub>	3	H	H	H	H	OCH <sub>3</sub>	H	H	CF <sub>3</sub>
1A	62N	CF <sub>3</sub>	3	H	H	H	CH <sub>3</sub>	H	H	H	CF <sub>3</sub>
1A	63N	CF <sub>3</sub>	3	H	H	H	Cl	H	H	H	CF <sub>3</sub>
1A	64N	CF <sub>3</sub>	3	H	H	H	CF <sub>3</sub>	H	H	H	OCF <sub>3</sub>

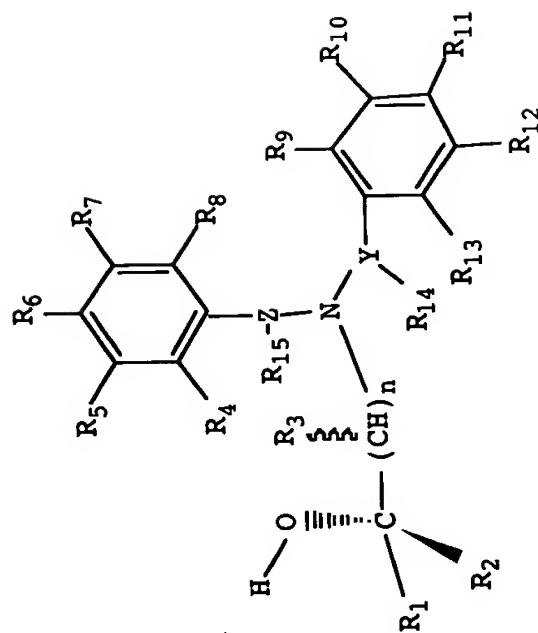
Table 6. (continued) Structure of Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols  
(Y is CH; R<sub>8</sub>, R<sub>9</sub>, R<sub>12</sub>, R<sub>13</sub>, and R<sub>14</sub> are each H; Z is covalent bond and R<sub>15</sub> is absent).

Inhibitor Number Column1+Column 2		R <sub>1</sub>	n	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	R <sub>6</sub>	R <sub>7</sub>	R <sub>10</sub>	R <sub>11</sub>
Reagent	Reagent										
1A	65N	CF <sub>3</sub>	3	H	H	H	F	H	H	H	OCF <sub>3</sub>
1A	66N	CF <sub>3</sub>	3	H	H	H	F	H	F	H	OCF <sub>3</sub>
1A	67N	CF <sub>3</sub>	3	H	H	H	Br	H	H	H	OCF <sub>3</sub>
1A	68N	CF <sub>3</sub>	3	H	H	H	Cl	H	H	H	OCF <sub>3</sub>
1A	69N	CF <sub>3</sub>	3	H	H	H	F	F	H	H	OCF <sub>3</sub>
1A	70N	CF <sub>3</sub>	3	H	H	H	F	H	H	H	phenyl
1A	71N	CF <sub>3</sub>	3	H	H	H	CH <sub>3</sub>	H	H	H	OCF <sub>3</sub>
1A	72N	CF <sub>3</sub>	3	H	H	H	F	F	H	H	CF <sub>3</sub>
1A	73N	CF <sub>3</sub>	3	H	H	H	Cl	H	H	H	CH <sub>3</sub>
1A	74N	CF <sub>3</sub>	3	H	H	H	OCH <sub>3</sub>	H	H	H	CH <sub>3</sub>
1A	75N	CF <sub>3</sub>	3	H	H	H	F	H	H	H	CH <sub>3</sub>
1A	76N	CF <sub>3</sub>	3	H	H	H	F	H	H	H	OCF <sub>3</sub>

Table 6. (continued) Structure of Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols  
(Y is CH; R<sub>8</sub>, R<sub>9</sub>, R<sub>12</sub>, R<sub>13</sub>, and R<sub>14</sub> are each H; Z is covalent bond and R<sub>15</sub> is absent).

<u>Inhibitor Number</u> <u>Column 1+Column 2</u>		<u>R<sub>1</sub></u>	<u>n</u>	<u>R<sub>2</sub></u>	<u>R<sub>3</sub></u>	<u>R<sub>4</sub></u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>7</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>
Reagent	Reagent										
1A	78N	CF <sub>3</sub>	3	H	H	H	H	OCH <sub>3</sub>	H	H	CH <sub>3</sub>
1A	79N	CF <sub>3</sub>	3	H	H	H	H	CH <sub>3</sub>	H	H	CH <sub>3</sub>
1A	80N	CF <sub>3</sub>	3	H	H	H	CH <sub>3</sub>	H	H	H	CH <sub>3</sub>
1A	82N	CF <sub>3</sub>	3	H	H	H	F	F	H	H	CH <sub>3</sub>
1A	83N	CF <sub>3</sub>	3	H	H	H	F	H	F	H	CH <sub>3</sub>
1A	84N	CF <sub>3</sub>	3	H	H	F	F	H	H	H	CH <sub>3</sub>
1A	85N	CF <sub>3</sub>	3	H	H	F	CF <sub>3</sub>	H	H	H	CH <sub>3</sub>
1A	86N	CF <sub>3</sub>	3	H	H	H	H	CH <sub>3</sub>	H	H	CF <sub>3</sub>
1A	88N	CF <sub>3</sub>	3	H	H	H	CF <sub>3</sub>	H	H	H	CH <sub>3</sub>
1A	90N	CF <sub>3</sub>	3	H	H	H	H	CF <sub>3</sub>	H	H	CH <sub>3</sub>
1A	92N	CF <sub>3</sub>	3	H	H	H	CF <sub>3</sub>	F	H	H	CH <sub>3</sub>

Table 7. Structure of Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols  
(Y and Z are each CH; R<sub>8</sub>, R<sub>9</sub>, R<sub>12</sub>, R<sub>13</sub>, R<sub>14</sub> and R<sub>15</sub> are each H).



Inhibitor Number		R <sub>1</sub>	n	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	R <sub>6</sub>	R <sub>9</sub>	R <sub>10</sub>	R <sub>11</sub>
Column 1+Column 2											
Reagent	Reagent										
IA	IDB	CF <sub>3</sub>	3	H	H	H	OCF <sub>3</sub>	H	H	OCF <sub>3</sub>	H

Table 7. (continued) Structure of Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols  
(Y and Z are each CH; R<sub>8</sub>, R<sub>9</sub>, R<sub>12</sub>, R<sub>13</sub>, R<sub>14</sub> and R<sub>15</sub> are each H).

Inhibitor Number Column 1+Column 2		R <sub>1</sub>	n	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	R <sub>6</sub>	R <sub>9</sub>	R <sub>10</sub>	R <sub>11</sub>
Reagent	Reagent										
1A	2DB	CF <sub>3</sub>	3	H	H	H	Cl	H	H	H	CF <sub>3</sub>
1A	3DB	CF <sub>3</sub>	3	H	H	H	Br	H	H	OCF <sub>3</sub>	H
1A	4DB	CF <sub>3</sub>	3	H	H	H	Cl	H	H	OCF <sub>3</sub>	H
1A	5DB	CF <sub>3</sub>	3	H	H	H	Cl	H	H	CF <sub>3</sub>	H
1A	6DB	CF <sub>3</sub>	3	H	H	H	H	Cl	H	CF <sub>3</sub>	H
1A	7DB	CF <sub>3</sub>	3	H	H	H	F	H	H	OCF <sub>3</sub>	H
1A	8DB	CF <sub>3</sub>	3	H	H	H	H	Cl	H	H	CF <sub>3</sub>
1A	9DB	CF <sub>3</sub>	3	H	H	H	F	H	H	H	CF <sub>3</sub>
1A	10DB	CF <sub>3</sub>	3	H	H	H	H	F	H	H	CF <sub>3</sub>
1A	11DB	CF <sub>3</sub>	3	H	H	F	H	H	H	H	CF <sub>3</sub>
1A	12DB	CF <sub>3</sub>	3	H	H	H	Cl	H	CF <sub>3</sub>	H	H

Table 7. (continued) Structure of Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols  
(Y and Z are each CH; R<sub>8</sub>, R<sub>9</sub>, R<sub>12</sub>, R<sub>13</sub>, R<sub>14</sub> and R<sub>15</sub> are each H).

Inhibitor Number Column 1+Column 2	R <sub>1</sub>	n	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	R <sub>6</sub>	R <sub>9</sub>	R <sub>10</sub>	R <sub>11</sub>
Reagent										
1A	13DB	3	H	H	H	H	Cl	CF <sub>3</sub>	H	H
1A	14DB	3	H	H	Cl	H	H	CF <sub>3</sub>	H	H
1A	15DB	3	H	H	H	F	H	CH <sub>3</sub>	H	H
1A	16DB	3	H	H	H	H	F	H	H	CH <sub>3</sub>
1A	17DB	3	H	H	H	F	H	H	CH <sub>3</sub>	H
1A	18DB	3	H	H	F	H	H	CH <sub>3</sub>	H	H
1A	19DB	3	H	H	H	H	F	H	CH <sub>3</sub>	H
1A	20DB	3	H	H	F	H	H	H	H	CH <sub>3</sub>
1A	21DB	3	H	H	F	H	H	H	CF <sub>3</sub>	H
1A	22DB	3	H	H	Cl	H	H	H	CF <sub>3</sub>	H
1A	23DB	3	H	H	H	F	H	CF <sub>3</sub>	H	H

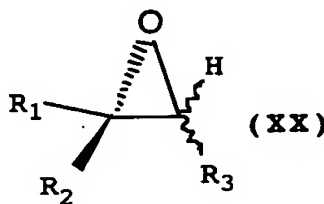
Table 7. (continued) Structure of Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols  
(Y and Z are each CH; R<sub>8</sub>, R<sub>9</sub>, R<sub>12</sub>, R<sub>13</sub>, R<sub>14</sub> and R<sub>15</sub> are each H).

<u>Inhibitor Number</u> <u>Column 1+Column 2</u>		<u>R<sub>1</sub></u>	<u>n</u>	<u>R<sub>2</sub></u>	<u>R<sub>3</sub></u>	<u>R<sub>4</sub></u>	<u>R<sub>5</sub></u>	<u>R<sub>6</sub></u>	<u>R<sub>9</sub></u>	<u>R<sub>10</sub></u>	<u>R<sub>11</sub></u>
Reagent	Reagent										
1A	24DB	CF <sub>3</sub>	3	H	H	H	H	F	CF <sub>3</sub>	H	H
1A	25DB	CF <sub>3</sub>	3	H	H	H	F	H	H	CF <sub>3</sub>	H
1A	26DB	CF <sub>3</sub>	3	H	H	H	H	F	H	CF <sub>3</sub>	H
1A	27DB	CF <sub>3</sub>	3	H	H	H	OCF <sub>3</sub>	H	H	H	OCF <sub>3</sub>



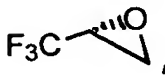
Formula I-H ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-alkanols"), Formula I-HP ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-propanols"), Formula I-HPC ("Polycyclic Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols"), Formula I-C ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols"), and Formula I-CP ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") compounds can also be prepared using Method B of Scheme 2 through the use of racemic (XXX) as described followed by preparative separation of the R-enantiomer from the S-enantiomer using chiral chromatographic procedures such as preparative gas chromatography and high pressure liquid chromatography using readily available chiral chromatographic columns and procedures.

A preferred procedure for Formula I-HP ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-propanols"), Formula I-HPC ("Polycyclic Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols"), and Formula I-CP ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") compounds is the novel inventive Method A of Scheme 2. (R)-Chiral oxirane reagents useful in Method A are exemplified, but not limited to those in Table 1. Formula I-HP ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-propanols"), Formula I-HPC ("Polycyclic Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols"), and Formula I-CP ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") compounds are prepared by reacting "Generic Secondary Amine" amines, hydroxylamines, and hydrazines of Formula XIII with (R)-chiral oxiranes of the type listed in Table 1 and represented by the general structure:



Oxiranes having a specific stereochemical arrangement of  $R_1$ ,  $R_2$  and  $R_3$  can be prepared using chiral procedures such as those published in 1995 by

Ramachandran, Gong, and Brown in the Journal of Organic Chemistry, Vol. 60, pages 41 to 46; cited references also detail alternate procedures to prepare chiral and achiral epoxides, which are incorporated herein by reference. For example, the specific preparation of *R*-(+)-1,1,1-trifluoro-2,3-epoxypropane,

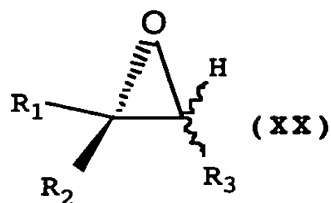
- 5 , using a procedure adopted from H.C.Brown et al. (*J. Org. Chem.* **60**, 41-46, (1995)), is accomplished as described in **Example 4**. Many of the epoxides summarized in Table 1 can be prepared in the (*R*)-configuration using procedures analogous to that given above for *R*-(+)-1,1,1-trifluoro-2,3-epoxypropane.
- 10 In some cases, achiral oxiranes of (XX) can be prepared from the corresponding alkenes by reaction of epoxidation reagents such as meta-chloroperbenzoic acid (MCPBA) and similar type reagents readily selectable by a person of skill-in-the-art with alkenes. Fieser and Fieser in Reagents for Organic Synthesis, John Wiley & Sons provides, along with cited references,
- 15 numerous suitable epoxidation reagents and reaction conditions, which are incorporated herein by reference. These achiral oxiranes can be reacted in an identical manner to that described for (*R*)-chiral oxiranes with "Generic Secondary Amine" amines, hydroxylamines, and hydrazines of Formula XIII to afford racemic compounds structurally identical to those of Formula I-HP,
- 20 Formula I-HPC, and Formula I-C but with the corresponding (*S*) chiral configuration present in an equivalent amount. Formula I-HP ("Generic Polycyclic Aryl and Heteroaryl (*R*)-Chiral Halogenated 1-Substitutedamino-2-propanols"), Formula I-HPC ("Polycyclic Aryl-Heteroaryl (*R*)-Chiral Halogenated 1-Substitutedamino-2-Propanols"), and Formula I-CP
- 25 ("Polycyclic Phenyl (*R*)-Chiral Halogenated 1-Substitutedamino-2-Propanols") compounds can be obtained by preparative chiral chromatography of said racemic mixtures to obtain the (*R*)-chiral configuration of Formula I-HP, Formula I-HPC, and Formula I-CP substantially free of the (*S*)-chiral configuration enantiomer. Alternatively, achiral oxiranes may be separated by
- 30 chiral preparative chromatography into their respective (*R*)-Chiral and (*S*)-Chiral enantiomers and the (*R*)-Chiral enantiomer reacted to afford Formula I-HP ("Generic Polycyclic Aryl and Heteroaryl (*R*)-Chiral Halogenated 1-Substitutedamino-2-propanols"), Formula I-HPC ("Polycyclic Aryl-Heteroaryl

(R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”), and Formula I-CP (“Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”) compounds.

- 5 A mixture of a “Generic Secondary Amine” amine, hydroxylamine, or hydrazine of Formula XIII and an excess of a halogenated oxirane of (R)-chiral configuration of Formula XX are stirred and heated to 40-90°C for 5 to 48 hours in a tightly capped or contained reaction vessel. More preferably, a Lewis acid such as a transition metal-based salts (for example, ytterbium triflate, hafnium triflate, scandium triflate, neodymium triflate, gadolinium triflate, 10 and zirconium triflate) in methylene chloride, tetrahydrofuran, or, more preferably, acetonitrile is added to speed up the reaction to a total time of 4 to 18 hours, improve yields, to permit the reaction temperature to be reduced to 15-65°C, and to use a smaller excess of halogenated oxirane. When a Lewis acid is used, the reaction should be carried out under inert, anhydrous 15 conditions using a blanket of dry nitrogen or argon gas. After cooling to room temperature and testing the reaction mixture for complete reaction by thin layer chromatography or high pressure liquid chromatography (hplc), the reaction product is added to water and extracted with a water immiscible solvent such as diethyl ether or methylene chloride. (Note: If the above analysis indicates that 20 reaction is incomplete, heating should be resumed until complete with the optional addition of more of the oxirane). The combined aprotic solvent extract is washed with saturated brine, dried over drying agent such as anhydrous MgSO<sub>4</sub> and concentrated *in vacuo* to yield crude Formula I-HP (“Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-propanols”), Formula I-HPC (“Polycyclic Aryl-Heteroaryl (R)-Chiral 25 Halogenated 1-Substitutedamino-2-Propanols”), and Formula I-C (“Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”) compounds. This material is purified by eluting through silica gel with 5-40% of a medium polar solvent such as ethyl acetate in a non-polar solvent such as hexanes to 30 yield Formula I-HP (“Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-propanols”), Formula I-HPC (“Polycyclic Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”), and Formula I-C (“Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”) compounds. Products are tested for purity by

- HPLC. If necessary, the Formula I-HP ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-propanols"), Formula I-HPC ("Polycyclic Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols"), and Formula I-C ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") compounds are purified
- 5 by additional chromatography or recrystallization. Products are structurally confirmed by low and high resolution mass spectrometry and NMR. Examples of specific Formula I-HP ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-propanols"), Formula I-HPC ("Polycyclic Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols"),
- 10 and Formula I-C ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") compounds prepared are summarized in the Examples 1 through 44, and Example Tables 1 through 12.

Table 1. Structure of (R)-Chiral Oxirane Reagents.

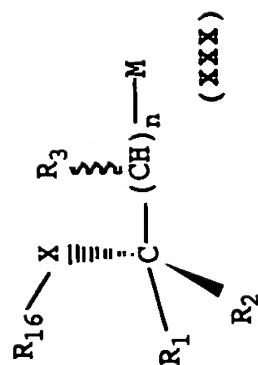


Reagent Number	<u>R<sub>1</sub></u>	<u>R<sub>2</sub></u>	<u>R<sub>3</sub></u>
1	CF <sub>3</sub>	H	H
2	CCl <sub>3</sub>	H	H
3	CF <sub>3</sub>	CH <sub>3</sub>	H
4	CF <sub>3</sub> CF <sub>2</sub>	H	H
5	CF <sub>3</sub> CF <sub>2</sub> CF <sub>2</sub>	H	H
6	CF <sub>3</sub> OCF <sub>2</sub> CF <sub>2</sub>	H	H
7	CF <sub>3</sub> CH <sub>2</sub>	H	H
9	CF <sub>3</sub>	H	CF <sub>3</sub>
11	CF <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	H
12	CCl <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	H
13	CCl <sub>3</sub>	Cyclopropyl	H
14	CCl <sub>3</sub>	CH <sub>3</sub>	H
15	CCl <sub>3</sub>	(CH <sub>3</sub> ) <sub>2</sub> CH	H
16	CHCl <sub>2</sub>	H	H
18	CF <sub>3</sub>	H	CH <sub>3</sub>
27	CCl <sub>3</sub> CH <sub>2</sub>	H	H
28	CBr <sub>3</sub> CH <sub>2</sub>	H	H
29	CHBr <sub>2</sub> CH <sub>2</sub>	H	H
30	CBrCl <sub>2</sub>	H	H
31	CClF <sub>2</sub>	H	H
32	CCl <sub>2</sub> F	H	H

Table 1. (continued) Structure of (R)-Chiral Oxirane Reagents.

<u>Reagent Number</u>	<u>R<sub>1</sub></u>	<u>R<sub>2</sub></u>	<u>R<sub>3</sub></u>
33	CCl <sub>3</sub> CCl <sub>2</sub>	H	H
43	FCH <sub>2</sub>	H	H
56	CBrF <sub>2</sub> CClFCH <sub>2</sub>	H	H
57	HCF <sub>2</sub> CF <sub>2</sub> OCH <sub>2</sub>	H	H

Table 2. Structure and Source of Alcohol and Glycol Reagents.



<u>Reagent Number</u>	<u>R<sub>1</sub></u>	<u>n</u>	<u>M</u>	<u>R<sub>2</sub></u>	<u>R<sub>3</sub></u>	<u>X-R<sub>16</sub></u>	<u>Source of Reagent</u>
1A	CF <sub>3</sub>	3	OTs	H	H	OH	Chiral separation and then tosylation of alcohol from Justus Liebigs Ann. Chem. (1969), 720, 81-97.
2A	CF <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub>	3	OTs	H	H	OH	Chiral separation and then tosylation of alcohol from Z. Naturforsch., B: Chem. Sci. (1997), 52 (3). 413-418

As summarized in the general Scheme 2 and specific descriptions above, Schemes 5, 6, 7, and 11 illustrate the principles of Scheme 2 for the preparation of specifically substituted Formula I-C ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") having 2 aryl groups, Formula I-HP ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-propanols") having two aromatic substituents made up of 0 to 2 aryl groups and 0 to 2 aromatic heterocyclyl groups, and Formula I-HPC ("Polycyclic Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") having two aromatic substituents made up of 0 to 2 aryl groups and 0 to 2 aromatic heterocyclyl groups.

Formula I-HP ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-propanols"), Formula I-HPC ("Polycyclic Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols"), and Formula I-C ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") compounds can further be prepared in an alternate manner to procedures disclosed above and in Schemes 1 to 7 and 9 to 11. Schemes 45 to 50 detail such procedures to prepare aminopropanol compounds of the present invention by initial formation of an halogenated, oxygen containing primary alkylamine XVL ("Generic Substituted Alkylamine"). Said halogenated, oxygen containing primary alkylamine XVL, formed in Schemes 45 and 48, is itself converted to secondary amines, VLX-H ("Heteroaryl Alkyl Amine) and VLX ("Phenyl Alkyl Amine"), using procedures disclosed above. Primary alkylamine XVL is first reacted with an aldehydic or ketonic carbonyl compound, XI-AH ("Heteroaryl Carbonyl") and XI-A ("Phenyl Carbonyl") with azeotropic distillation to form imines, VL-H ("Heteroaryl Imine") and VL ("Phenyl Imine"). Said imines VL-H and VL are then reduced with or without prior isolation by Reduction Methods 1, 2 or 3 as disclosed above and in Schemes 1, 3, and 9 to yield secondary amines, VLX-H ("Heteroaryl Alkyl Amine) and VLX ("Phenyl Alkyl Amine"). Said secondary amine VLX-H can be converted according to Schemes 46 and 47 to give Formula I-HP ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-propanols") and Formula I-HPC ("Polycyclic Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-



Propanols”) and Formula I-C (“Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”) compounds. Using Schemes 49 and 50, VLX can be converted to Formula I-C (“Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”) compounds. Compounds of this invention in which one aromatic substituent is aryl and the other aromatic substituent is heteroaryl can be readily prepared by reacting VLX-H with an aralkyl bromide or aryl bromide instead of using an heteroaralkyl bromide or heteroaryl bromide as described in Schemes 46 and 47. Similarly, compounds of this invention in which one aromatic substituent is aryl and the other aromatic substituent is heteroaryl can be readily prepared by reacting VLX with an heteroaryl bromide or heteroaralkyl bromide instead of using an aryl bromide or an aralkyl bromide as described in Schemes 49 and 50.

Formula I-HP (“Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-propanols”), Formula I-HPC (“Polycyclic Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”), and Formula I-C (“Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”) compounds can further be prepared in an alternate manner to procedures disclosed above and in Schemes 1 to 7, 9 to 11, and 45 to 50. Schemes 56,57, and 58 detail alternate procedures to prepare (R)-Chiral Halogenated 1-Substitutedamino-2-propanols” compounds of the present invention by initial formation of an halogenated, oxygen containing secondary alkylamines VLX and VLXX (“Phenyl Alkylamines”) and VLXX-O (“Phenyl Oxy Alkylamines”). Said secondary alkylamines VLX and VLXX (“Phenyl Alkylamines”) and VLXX-O (“Phenyl Oxy Alkylamines”) can be converted according to Schemes 56,57, and 58 to Formula I-HP (“Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-propanols”), Formula I-HPC (“Polycyclic Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”), and Formula I-C (“Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”) compounds by reaction with appropriate aromatic halides such as aryl bromides and heteroaryl bromides as desired.

Formula I-HP (“Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-propanols”), Formula I-HPC (“Polycyclic Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”),

and Formula I-C ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") compounds can further be prepared in an alternate manner to procedures disclosed above and in Schemes 1 to 7, 9 through 11, 45 through 50, and 56 through 58. Another alternate procedure to prepare "(R)-Chiral Halogenated 1-Substitutedamino-2-propanols" compounds of the present invention can be achieved by reacting secondary amines of Formula XIII-A-H ("Secondary Heteroaryl Amines") and Formula XIII-A ("Secondary Phenyl Amines") with certain cyclic sulfates. Cyclic sulfates useful in the preparation of "(R)-Chiral Halogenated 1-Substitutedamino-2-propanols" compounds of Formulas I-HP, I-HPC, and I-CP have a halogenated or haloalkoxy carbon adjacent to the cyclic sulfate. Some cyclic sulfates useful for the preparation of "(R)-Chiral Halogenated 1-Substitutedamino-2-propanols" compounds of Formulas I-HP, I-HPC, and I-CP have been described by K. P. M. Vanhessche and K. B. Sharpless in Chem. Eur. J, 1997, Vol. 3, No. 4, pages 517-522 and references cited therein. (2R)-(+)-3,3,3-Trifluoro-1,2-propanediol can be prepared as described in the reference cited immediately above from 3,3,3-trifluoropropene followed by separation from the predominating (2S)-(-)-3,3,3-trifluoro-1,2-propanediol. Alternatively, (2R)-(+)-3,3,3-Trifluoro-1,2-propanediol can be prepared by hydrolysis of (2R)-(+)-3,3,3-Trifluoro-2,3-epoxypropane analogous to the procedure described by described by McBee and Burton in J. Am. Chem. Soc., 1952, Vol. 74, page 3022. (2R)-(+)-3,3,3-Trifluoro-1,2-propanediol is converted by reaction with a slight excess of sulfuryl chloride in the presence of 2.5 molar equivalents of imidazole, methylene chloride solvent, and at a temperature of -20 °C to give the desired (4R)-(+)-4-trifluoromethyl-2,2-dioxo-1,3,2-dioxathiolane. Reaction of other (R)-Chiral haloalkyl or haloalkoxyalkyl substituted 1,2-ethanediols can afford the corresponding (4R)-substituted-2,2-dioxo-1,3,2-dioxathiolanes. Reaction of (4R)-(+)-4-trifluoromethyl-2,2-1,3,2-dioxathiolane or another (4R)-substituted-2,2-dioxo-1,3,2-dioxathiolane with a secondary amine of Formula XIII-A-H ("Secondary Heteroaryl Amines") and Formula XIII-A ("Secondary Phenyl Amines") in an anhydrous polar, non-protic solvent such as tetrahydrofuran or acetonitrile at 25-60 °C until the reaction is complete can afford the mono-sulfate ester of a

compound of Formulas I-HP, I-HPC, and I-CP. Removal of the solvent followed by addition of diethyl ether and excess 20% aqueous sulfuric acid can lead to a precipitant of the crude mono-sulfate ester of a compound of Formulas I-HP, I-HPC, and I-CP. This precipitant can be filtered, the solid can be washed with ether, it can be resuspended in aqueous 20% sulfuric acid, and can be heated to 80-95 °C to give an aqueous solution of the sulfate salt of crude a compound of Formulas I-HP, I-HPC, and I-CP. Neutralization of the aqueous solution, extraction with a water immiscible solvent such as diethyl ether or methylene chloride, drying the organic solvent over anhydrous magnesium sulfate, and removal of solvent can afford a compound of Formulas I-HP, I-HPC, and I-CP. Compounds of Formulas I-HP, I-HPC, and I-CP can be purified as described previously. By using a wide variety of (R)-Chiral diols, secondary amines of Formula XIII-A-H ("Secondary Heteroaryl Amines") and Formula XIII-A ("Secondary Phenyl Amines"), and reaction conditions described herein, a large variety of compounds of Formulas I-HP, I-HPC, and I-CP may be preparable.

Formula I-H ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-alkanols") and Formula I-C ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols"), in which the halogenated hydroxy containing alkyl side chain has three carbons between the amine and hydroxy group, can be prepared in a manner similar to procedures disclosed above and in Schemes 45 to 50. Schemes 30 to 35 detail such procedures to prepare 1-amino-3-butanol compounds of the present invention by initial formation of an halogenated, oxygen containing primary alkylamine XL ("Generic Substituted Alkylamine"). Said halogenated, oxygen containing primary alkylamine XL, formed in Schemes 30 and 33, is itself converted to secondary amines, LX-H ("Heteroaryl Alkyl Amine) and LX ("Phenyl Alkyl Amine"), using procedures disclosed above. Primary alkylamine XL is first reacted with an aldehydic or ketonic carbonyl compound, XI-AH ("Heteroaryl Carbonyl") and XI-A ("Phenyl Carbonyl") with azeotropic distillation to form imines, L-H ("Heteroaryl Imine") and L ("Phenyl Imine"). Said imines L-H and L are then reduced with or without prior isolation by Reduction Methods 1, 2 or 3 as disclosed above and in Schemes 1, 3, and 9 to yield secondary amines, LX-H

("Heteroaryl Alkyl Amine) and LX ("Phenyl Alkyl Amine"). Said secondary amine LX-H can be converted according to Schemes 31 and 32 to Formula I-H ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-alkanols"). Using Schemes 34 and 35, LX can be  
 5 converted to Formula I-C ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols"). Compounds of this invention in which one aromatic substituent is aryl and the other aromatic substituent is heteroaryl can be readily prepared by reacting LX-H with an aryl bromide instead of using an heteroaryl bromide as described in Schemes 31 and 32. Similarly,  
 10 compounds of this invention in which one aromatic substituent is aryl and the other aromatic substituent is heteroaryl can be readily prepared by reacting LX with an heteroaryl bromide instead of using an aryl bromide as described in Schemes 34 and 35.

Particularly useful procedures to prepare Formula I-H ("Generic  
 15 Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-alkanols"), Formula I-HP ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated I-Substitutedamino-2-propanols"), Formula I-HPC ("Polycyclic Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols"), Formula I-C ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols"), and Formula I-CP ("Polycyclic Phenyl  
 20 (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") compounds of the present invention in which the heteroaryl group is directly bonded is disclosed in Schemes 51 to 54. An halogenated, hydroxy containing primary alkylamine XVL ("Generic Substituted Alkylamine") formed in Schemes 45 and 48 is  
 25 itself converted by reaction with LXXI-AH ("Heteroaryl Halide") to afford secondary amine VLXX-H ("Heteroaryl Secondary Amine) using procedures disclosed in Scheme 51 and above. VLXX-H is converted to Formula I-HP ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated I-Substitutedamino-2-propanols"), Formula I-HPC ("Polycyclic Aryl-Heteroaryl  
 30 (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols"), and Formula I-CP ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") compounds by alkylation chemistry with an aralkyl bromide or aralkyloxyalkyl bromide using either of two procedures disclosed in Scheme 52. Isolation and purification is effected as disclosed previously. An halogenated, hydroxy

containing primary alkylamine XL ("Generic Substituted Alkylamine") formed in Schemes 30 and 33 is itself also converted by reaction with LXXI-AH ("Heteroaryl Halide") to afford secondary amine LXX-H ("Heteroaryl Secondary Amine") using procedures disclosed in Scheme 53 and above. LXX-H is converted to Formula I-H ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-alkanols") and Formula I-C ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols") compounds by alkylation chemistry disclosed in Scheme 54 and previously and as given above with reference to Scheme 52. Isolation and purification of I-H and I-C are effected as disclosed previously.

Formula I-H ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-alkanols"), Formula I-HP ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-propanols"), Formula I-HPC ("Polycyclic Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols"), Formula I-C ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols"), and Formula I-CP ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") compounds can themselves serve as intermediates for conversion to additional compounds of this invention.

Compounds of Formulas I-H, I-HP, I-C, I-CP, I-HPC and others of the present invention useful as intermediates include those in which the R<sub>7</sub> position substituent in Formulas I-H, I-HP, I-C, I-CP, and I-HPC is a bromo group, hydroxyl group, sulfhydryl group, bromomethyl or other bromoalkyl groups, nitro group, amino group, methoxycarbonyl or other alkoxy carbonyl groups, cyano group, or acyl group. Other preferred compounds of Formulas I-H, I-HP, I-C, I-CP, I-HPC and the present invention useful as intermediates include those in which the R<sub>10</sub> position substituent is a bromo group, hydroxyl group, sulfhydryl group, bromomethyl or other bromoalkyl groups, nitro group, amino group, methoxy carbonyl or other alkoxy carbonyl groups, cyano group, or acyl groups. Other compounds of Formulas I-H, I-HP, I-C, I-CP, I-HPC and the present invention useful as intermediates include those in which one or more of R<sub>6</sub>, R<sub>7</sub>, R<sub>11</sub>, and R<sub>12</sub> substituents in Formula VII is a bromo group, hydroxyl group, sulfhydryl group, bromomethyl or other

bromoalkyl groups, nitro group, amino group, methoxy carbonyl or other alkoxy carbonyl groups, cyano group, or acyl groups.

Scheme 8 discloses the conversion of a 3-bromo substituent at the R<sub>7</sub> position in Formula I-CP ("Polycyclic 3-Bromophenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") compounds by reaction with a phenol to afford, after isolation and purification as described above for Schemes 2, 5, 6, 7, and 11, additional compounds of the present invention of Formula I-CP ("Polycyclic 3-Phenoxyphenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols").

Scheme 12 discloses the conversion of a 3-bromo substituent at the R<sub>7</sub> position in Formula I-HP and I-HPC ("Polycyclic 3-Bromophenyl and 3-Bromoheteroaryl/Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") by reaction with a phenol or thiophenol to afford, after isolation and purification as described above for Schemes 2, 5, 6, 7, and 11, additional compounds of the present invention of Formula I-HP and I-HPC ("Polycyclic 3-Aryloxyaryl, 3-Heteroaryloxyaryl, 3-Heteroaryloxyheteroaryl, 3-Aryloxyheteroaryl, 3-Arylthioaryl, 3-Heteroarylthioaryl, 3-Heteroarylthioheteroaryl, and 3-Arylthioheteroaryl Aryl and Heteroaryl/Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols").

Scheme 22 discloses the conversion of a 3-bromo substituent at the R<sub>7</sub> position in Formula I-CP ("Polycyclic 3-Bromophenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") compounds by reaction with an aryl borinate or an aryl tin to afford, after isolation and purification as described above for Schemes 2, 5, 6, 7, and 11, additional compounds of the present invention of Formula I-CP ("Polycyclic 3-Arylphenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols").

Scheme 23 discloses the conversion of a 3-bromo substituent at the R<sub>7</sub> position in Formula I-CP ("Polycyclic 3-Bromophenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") compounds by reaction with a primary or secondary amine to afford, after isolation and purification as described above for Schemes 2, 5, 6, 7, and 11, additional compounds of the present invention of Formula I-CP ("Polycyclic 3- R<sub>22</sub>aminophenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols").

Scheme 40 discloses the conversion of a 3-bromo substituent at the R<sub>10</sub> position in Formula I-CP ("Polycyclic 3-Bromophenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") compounds by reaction with an aryl borinate to afford, after isolation and purification as described above for Schemes 2, 5, 6, 7, and 11, additional compounds of the present invention of Formula I-CP ("Polycyclic 3-Arylphenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols").

Scheme 41 discloses the conversion of a 3-bromo substituent at the R<sub>10</sub> position in Formula I-CP ("Polycyclic 3-Bromophenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") compounds by reaction with a heteroaryl dibutyl tin compound to afford, after isolation and purification as described above for Schemes 2, 5, 6, 7, and 11, additional compounds of the present invention of Formula I-CP ("Polycyclic 3-Heteroarylphenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols").

Scheme 21 discloses the conversion of a 3-bromomethyl substituent at the R<sub>7</sub> position in Formula I-CP ("Polycyclic 3-Bromomethylphenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") by reaction with an aryl borinate to afford, after isolation and purification as described above for Schemes 2, 5, 6, 7, and 11, additional compounds of the present invention of Formula I-CP ("Polycyclic 3-Arylmethylphenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols").

Scheme 13 discloses the conversion of a 3-hydroxyl substituent at the R<sub>7</sub> position in Formula I-HP and I-HPC ("Polycyclic 3-Hydroxyphenyl and 3-Hydroxyheteroaryl/Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") by reaction with an aryl bromide or heteroaryl bromide to afford, after isolation and purification as described above for Schemes 2, 5, 6, 7, and 11, additional compounds of the present invention of Formula I-HP and I-HPC ("Polycyclic 3-Aryloxyaryl, 3-Heteroaryloxyaryl, 3-Heteroaryloxyheteroaryl, and 3-Aryloxyheteroaryl Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols").

Scheme 14 discloses the conversion of a 3-hydroxyl substituent at the R<sub>7</sub> position in Formula I-CP ("Polycyclic 3-Hydroxyphenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") compounds by reaction with

an aryl bromide to afford, after isolation and purification as described above for Schemes 2, 5, 6, 7, and 11, additional compounds of the present invention of Formula I-CP ("Polycyclic 3-Phenoxyphenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols").

5            Scheme 15 discloses the conversion of a 3-hydroxyl substituent at the R<sub>7</sub> position in Formula I-HP and I-HPC ("Polycyclic 3-Hydroxyphenyl and 3-Hydroxyheteroaryl/Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") compounds by reaction with an aralkyl  
10           bromide or heteroaralkyl bromide to afford, after isolation and purification as described above for Schemes 2, 5, 6, 7, and 11, additional compounds of the present invention of Formula I-HP and I-HPC ("Polycyclic 3-Aralkyloxyaryl, 3-Heteroaralkyloxyaryl, 3-Heteroaralkyloxyheteroaryl, and 3-Aralkyloxyheteroaryl Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols").

15           Scheme 16 discloses the conversion of a 3-hydroxyl substituent at the R<sub>7</sub> position in Formula I-CP ("Polycyclic 3-Hydroxyphenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") compounds by reaction with  
an aralkyl bromide to afford, after isolation and purification as described above  
for Schemes 2, 5, 6, 7, and 11, additional compounds of the present invention  
20           of Formula I-CP ("Polycyclic 3-Aralkyloxyaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols").

             Scheme 20 discloses the conversion of a 3-hydroxyl substituent at the R<sub>7</sub> position in Formula I-CP ("Polycyclic 3-Hydroxyphenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") compounds by reaction with  
25           an R<sub>17</sub>-bromide to afford, after isolation and purification as described above for Schemes 2, 5, 6, 7, and 11, additional compounds of the present invention of Formula I-CP ("Polycyclic 3- R<sub>17</sub>-oxyaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols").

             Scheme 19 discloses the conversion of a 3-thio substituent at the R<sub>7</sub>  
30           position in Formula I-CP ("Polycyclic 3-thiophenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") compounds by reaction with an R<sub>17</sub>-bromide to afford, after isolation and purification as described above for Schemes 2, 5,



6, 7, and 11, additional compounds of the present invention of Formula I-CP (“Polycyclic 3- R<sub>17</sub>thiaaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”). “Polycyclic 3- R<sub>17</sub>thiaaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols” can be oxidized to sulfonyl compounds of  
5 Formula I-CP (“Polycyclic 3- R<sub>17</sub>sulfonylphenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”).

Scheme 24 discloses the conversion of a 3-nitro substituent at the R<sub>7</sub> position in Formula I-CP (“Polycyclic 3-Nitrophenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”) compounds by hydrogenation to afford,  
10 after isolation and purification as described above for Schemes 2, 5, 6, 7, and 11, additional compounds of the present invention of Formula I-CP (“Polycyclic 3-Aminophenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”). “Polycyclic 3-Aminophenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols” can be acylated to acyl amide compounds of  
15 Formula I-CP (“Polycyclic 3-R<sub>17</sub>-C(O)amidophenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”).

Schemes 25 and 26 disclose the conversion of a 3-amino substituent at the R<sub>7</sub> position in Formula I-CP (“Polycyclic 3-Aminophenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”) compounds by reaction with  
20 carbonyl compounds to afford, after isolation and purification as described above for Schemes 2, 5, 6, 7, and 11, additional compounds of the present invention of Formula I-CP (“Polycyclic 3-(Saturated Nitrogen Heterocycl-1yl)aryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols” and  
25 (“Polycyclic 3-(Unsaturated Nitrogen Heterocycl-1yl)aryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”, respectively).

Scheme 27 discloses the conversion of a 3-methoxycarbonyl substituent at the R<sub>7</sub> position in Formula I-CP (“Polycyclic 3-Carbomethoxyphenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”) compounds by reaction with amination reagents to afford, after  
30 isolation and purification as described above for Schemes 2, 5, 6, 7, and 11, additional compounds of the present invention of Formula I-CP (“Polycyclic 3-

Carboxamidophenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”).

Scheme 28 discloses the conversion of a 3-cyano substituent at the R<sub>7</sub> position in Formula I-CP (“Polycyclic 3-Cyanophenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”) compounds by reaction with organometallic reagents to afford, after isolation and purification as described above for Schemes 2, 5, 6, 7, and 11, additional compounds of the present invention of Formula I-CP (“Polycyclic 3-Acylphenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”). Said “Polycyclic 3-Acylphenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”, according to Scheme 29 can be reduced to hydroxyl compounds of Formula I-CP (“Polycyclic 3-hydroxysubstitutedmethylphenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”).

Scheme 36 discloses the conversion of a 3-methoxycarbonyl substituent at the R<sub>10</sub> position in Formula I-CP (“Polycyclic 3-Carbomethoxyphenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”) compounds by reaction with amination reagents to afford, after isolation and purification as described above for Schemes 2, 5, 6, 7, and 11, additional compounds of the present invention of Formula I-CP “Polycyclic 3-Carboxamdophenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”).

Scheme 37 discloses the conversion of a 3-methoxycarbonyl substituent at the R<sub>10</sub> position in Formula I-CP (“Polycyclic 3-Carbomethoxyphenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”) compounds by reaction with an organometallic reagent to afford, after isolation and purification as described above for Schemes 2, 5, 6, 7, and 11, additional compounds of the present invention of Formula I-CP “Polycyclic 3-(bis- R<sub>20</sub>-hydroxymethyl)aryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”).

Scheme 38 discloses the conversion of a 3-methoxycarbonyl substituent at the R<sub>10</sub> position in Formula I-CP (“Polycyclic 3-Carbomethoxyphenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols”) compounds by reaction with lithium aluminum hydride to afford,

after isolation and purification as described above for Schemes 2, 5, 6, 7, and 11, additional compounds of the present invention of Formula I-CP ("Polycyclic 3-Hydroxymethylphenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols").

- 5            Scheme 39 discloses the conversion of a 3-methoxycarbonyl substituent at the  $R_{10}$  position in Formula I-CP ("Polycyclic 3-Carbomethoxyphenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") compounds by reaction with an alkylation reagent to afford, after isolation and purification as described above for Schemes 2, 5, 6, 7, and 11, additional compounds of the present invention of Formula I-CP ("Polycyclic 3-(bis-  $R_{21}$ -hydroxymethyl)phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols").

- 10            Scheme 55 discloses the conversion of a 3-methoxycarbonyl substituent at the  $R_{10}$  position in Formula I-CP ("Polycyclic 3-Carbomethoxyphenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") compounds by reaction initially with an amidation reagent and then an  $R_{20}$ -organometallic reagent to afford, after isolation and purification as described above for Schemes 2, 5, 6, 7, and 11, additional compounds of the present invention of Formula I-CP ("Polycyclic 3-( $R_{20}$ -carbonyl)phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols").

- 15            Formula I-H ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-alkanols"), Formula I-HP ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-propanols"), Formula I-HPC ("Polycyclic Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols"), Formula I-C ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols"), and Formula I-CP ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") and other compounds of this invention possessing hydroxyl, thiol, and amine functional groups can be converted to a wide variety derivatives. The hydroxyl group, wherein  $R_{16}$  is a hydrogen and X is oxy, of compounds of Formulas I-H, I-HP, I-HPC, I-C, and I-CP can

be readily converted to esters of carboxylic, sulfonic, carbamic, phosphonic, and phosphoric acids. Acylation to form a carboxylic acid ester is readily effected using a suitable acylating reagent such as an aliphatic acid anhydride or acid chloride. The corresponding aryl and heteroaryl acid anhydrides and acid chlorides can also be used. Such reactions are generally carried out using an amine catalyst such as pyridine in an inert solvent. In like manner, compounds of Formulas I-H, I-HP, I-C, I-CP, I-HPC, Cyclo I-H, Cyclo I-C, and Cyclo I-CP that have at least one hydroxyl group present in the form of an alcohol or phenol can be acylated to its corresponding esters. Similarly, carbamic acid esters (urethans) can be obtained by reacting any hydroxyl group with isocyanates and carbamoyl chlorides. Sulfonate, phosphonate, and phosphate esters can be prepared using the corresponding acid chloride and similar reagents. Compounds of Formulas I-H, I-HP, I-C, I-CP, I-HPC, Cyclo I-H, Cyclo I-C, and Cyclo I-CP that have at least one thiol group present can be converted to the corresponding thioesters derivatives analogous to those of alcohols and phenols using the same reagents and comparable reaction conditions. Compounds of Formulas I-H, I-HP, I-C, I-CP, I-HPC, Cyclo I-H, Cyclo I-C, and Cyclo I-CP that have at least one primary or secondary amine group present can be converted to the corresponding amide derivatives. Amides of carboxylic acids can be prepared using the appropriate acid chloride or anhydrides with reaction conditions analogous to those used with alcohols and phenols. Ureas of the corresponding primary or secondary amine can be prepared using isocyanates directly and carbamoyl chlorides in the presence of an acid scavenger such as triethylamine or pyridine. Sulfonamides can be prepared from the corresponding sulfonyl chloride in the presence of aqueous sodium hydroxide. Suitable procedures and methods for preparing these derivatives can be found in House's Modern Synthetic Reactions, W. A. Benjamin, Inc., Shriner, Fuson, and Curtin in The Systematic Identification of Organic Compounds, 5th Edition, John Wiley & Sons, and Fieser and Fieser in Reagents for Organic Synthesis, Volume 1, John Wiley & Sons. Reagents of a wide variety that can be used to derivatize hydroxyl, thiol, and amines of compounds of Formulas I-H, I-HP, I-C, I-CP, I-HPC, Cyclo I-H, Cyclo I-C, and Cyclo I-CP are available from commercial sources or the references cited above, which are incorporated herein by reference.

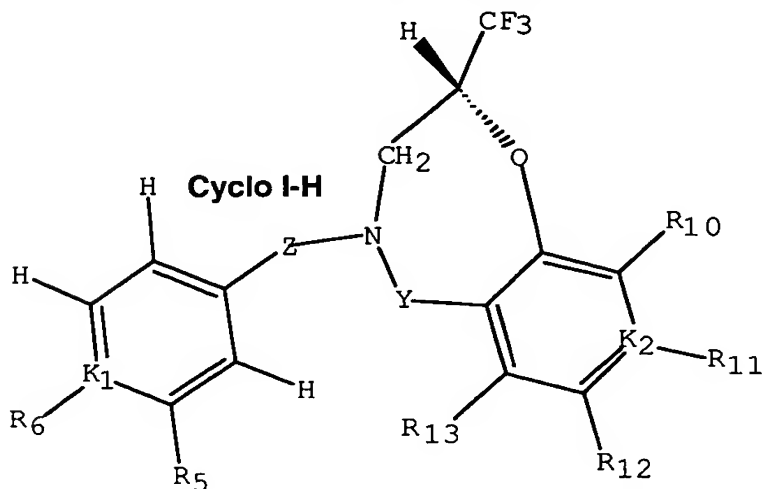
Formula I-H ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-alkanols"), Formula I-HP ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-propanols"), Formula I-HPC ("Polycyclic Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols"), Formula I-C ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols"), and Formula I-CP ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") and other compounds of this invention possesing hydroxyl, thiol, and amine functional groups can be alkylated to a wide variety derivatives. The hydroxyl group, wherein  $R_{16}$  is a hydrogen and X is oxy, of compounds of Formulas I-H, I-HP, I-C, I-CP, I-HPC, Cyclo I-H, Cyclo I-C, and Cyclo I-CP can be readily converted to ethers. Alkylation to form an ether is readily effected using a suitable alkylating reagent such as an alkyl bromide, alkyl iodide or alkyl sulfonate. The corresponding aralkyl, heteroaralkyl, alkoxyalkyl, aralkyloxyalkyl, and heteroaralkyloxyalkyl bromides, iodides, and sulfonates can also be used. Such reactions are generally carried out using an alkoxide forming reagent such as sodium hydride, potassium t-butoxide, sodium amide, lithium amide, and n-butyl lithium using an inert polar solvent such as DMF, DMSO, THF, and similar, comparable solvents. In like manner, compounds of Formulas I-H, I-HP, I-C, I-CP, I-HPC, Cyclo I-H, Cyclo I-C, and Cyclo I-CP that have at least one hydroxyl group present in the form of an alcohol or phenol can be alkylated to their corresponding ethers. Compounds of Formulas I-H, I-HP, I-C, I-CP, I-HPC, Cyclo I-H, Cyclo I-C, and Cyclo I-CP that have at least one thiol group present can be converted to the corresponding thioether derivatives analogous to those of alcohols and phenols using the same reagents and comparable reaction conditions. Compounds of Formulas I-H, I-HP, I-C, I-CP, I-HPC, Cyclo I-H, Cyclo I-C, and Cyclo I-CP that have at least one primary, secondary or tertiary amine group present can be converted to the corresponding quaternary ammonium derivatives. Quaternary ammonium derivatives can be prepared using the appropriate bromides, iodides, and sulfonates analogous to those used with alcohols and phenols. Conditions involve reaction of the amine by warming it

with the alkylating reagent with a stoichiometric amount of the amine (i.e., one equivalent with a tertiary amine, two with a secondary, and three with a primary). With primary and secondary amines, two and one equivalents, respectively, of an acid scavenger are used concurrently. Tertiary amines can be prepared from the corresponding primary or secondary amine by reductive alkylation with aldehydes and ketones using reduction methods 1, 2, or 3 as shown in Scheme 3. Suitable procedures and methods for preparing these derivatives can be found in House's Modern Synthetic Reactions, W. A. Benjamin, Inc., Shriner, Fuson, and Curtin in The Systematic Identification of Organic Compounds, 5th Edition, John Wiley & Sons, and Fieser and Fieser in Reagents for Organic Synthesis, Volume 1, John Wiley & Sons. Perfluoroalkyl derivatives can be prepared as described by DesMarteau in J. Chem. Soc. Chem. Commun. 2241 (1998). Reagents of a wide variety that can be used to derivatize hydroxyl, thiol, and amines of compounds of Formulas I-H, I-HP, I-C, I-CP, I-HPC, Cyclo I-H, Cyclo I-C, and Cyclo I-CP are available from commercial sources or the references cited above, which are incorporated herein by reference.

Formula I-H ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-alkanols"), Formula I-HP ("Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-propanols"), Formula I-HPC ("Polycyclic Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols"), Formula I-C ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols"), and Formula I-CP ("Polycyclic Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols") and certain other compounds of this invention can be converted, according to Schemes 17 and 18, to the corresponding cyclic derivatives represented by "Tricyclic *tertiary*-oxyalkylamines" and exemplified by Formulas Cyclo I-H ("Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated (N+1)-Cycloazaalkoxy"), Cyclo I-C ("Polycyclic Aryl Phenyl (R)-Chiral Halogenated (N+1)-Cycloazaalkoxy") and Cyclo I-CP ("Polycyclic Phenyl Phenyl (R)-Chiral Halogenated Cycloazaalkoxy"). The hydroxyl group, wherein R<sub>16</sub> is a hydrogen and X is oxy, of compounds of Formulas I-H, I-HP, I-C, I-CP, and I-HPC can be cyclized to corresponding cyclic ethers. Compounds suitable for cyclization will normally have at least one

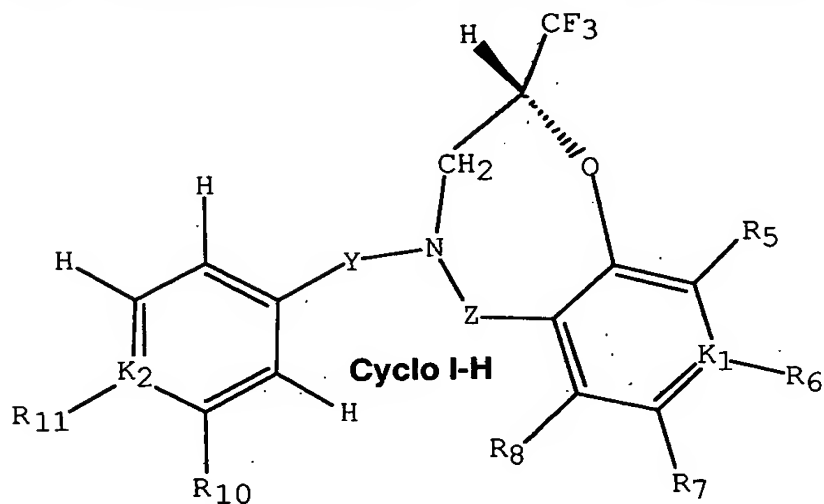
- leaving group within 5 to 10 continuous atoms of the hydroxyl group wherein  $R_{16}$  is a hydrogen and X is oxy. Most preferably the leaving group will be within 5 to 7 atoms of the hydroxyl group so as to form a 6 to 8 membered ring heteroatom containing ring. When the leaving group is part of an aromatic ring system, the leaving group will be preferably in an ortho position. Suitable leaving groups generally include halides, sulfates, sulfonates, trisubstituted amino, disubstituted sulfonium, diazonium, and like, and, in the case of aromatic systems, also includes nitro, alkoxy, aryloxy, heteroaryloxy, and alkylthio.
- 10 The cyclization reaction to form "Tricyclic *tertiary*-oxyalkylamines" of Formulas Cyclo I-H, Cyclo I-C and Cyclo I-CP can be accomplished by aromatic and aliphatic nucleophilic substitution reactions such as those disclosed in March's Advanced Organic Chemistry, 4th Edition, John Wiley & Sons, especially at pages 293-412 and 649-658 and the references cited
- 15 therein, which are incorporated herein by reference. Hydroxyl containing suitably substituted compounds can be converted to a cyclic analog by heating a suitably substituted compound under anhydrous conditions in a suitable solvent, such as dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone, tetraglyme, or hexamethylphosphoramide, in the presence of a suitable base
- 20 such as potassium carbonate, cesium carbonate, sodium hydroxide, potassium *tertiary*-butoxide, or lithium diisopropylamide. Alternately, sodium amide in anhydrous ammonia solvent can be used. Temperatures in the range of  $-20^{\circ}\text{C}$  to  $200^{\circ}\text{C}$  can be used for time periods of 30 minutes to more than 24 hours. The preferred temperature can be selected by standard synthetic chemical
- 25 technique balancing maximum yield, maximum purity, cost, ease of isolation and operation, and time required. Isolation of the "Tricyclic *tertiary*-oxyalkylamines" can be effected as described above for other *tertiary*-oxyalkylamines. Representative "Tricyclic *tertiary*-oxyalkylamines" prepared using the methodology described above are included in Table 8.
- 30 The following examples are provided to illustrate the present invention and are not intended to limit the scope thereof. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

Table 8. Structure of Substituted Tricyclictertiary-2-oxyalkylamines.



<u>Y</u>	<u>Z</u>	<u>R<sub>5</sub></u>	<u>K<sub>1</sub>-R<sub>6</sub></u>	<u>R<sub>10</sub></u>	<u>K<sub>2</sub>-R<sub>11</sub></u>	<u>R<sub>12</sub></u>	<u>R<sub>13</sub></u>
CH <sub>2</sub>	-	4-chloro-3-ethylphenoxy	C-H	H	C- CF <sub>3</sub>	H	H
CH <sub>2</sub>	-	4-chloro-3-ethylphenoxy	N	H	C- CF <sub>3</sub>	H	H
CH <sub>2</sub>	-	4-chloro-3-ethylphenoxy	C-H	H	C- H	CF <sub>3</sub>	H
CH <sub>2</sub>	-	4-chloro-3-ethylphenoxy	N	H	C- H	CF <sub>3</sub>	H
CH <sub>2</sub>	-	4-chloro-3-ethylphenoxy	C-H	H	N	CF <sub>3</sub>	H
-	-	4-chloro-3-ethylphenoxy	C-H	H	C- CF <sub>3</sub>	H	H
-	-	4-chloro-3-ethylphenoxy	N	H	C- CF <sub>3</sub>	H	H
-	-	4-chloro-3-ethylphenoxy	C-H	H	C- H	CF <sub>3</sub>	H
-	-	4-chloro-3-ethylphenoxy	N	H	C- H	CF <sub>3</sub>	H
-	-	4-chloro-3-ethylphenoxy	C-H	H	N	CF <sub>3</sub>	H



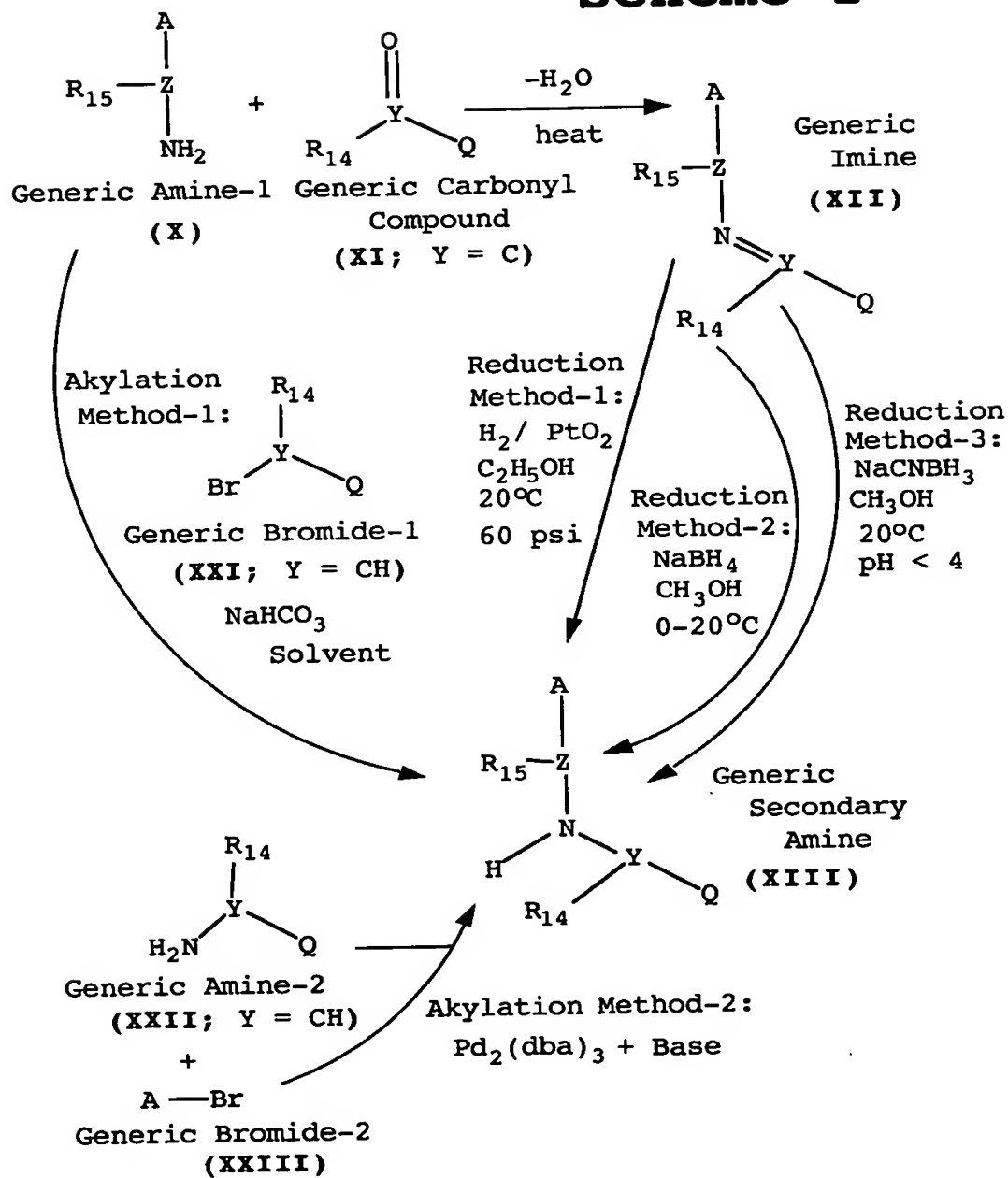
Table 8. (cont.) Structure of Substituted Tricyclic *tertiary*-2-oxyalkylamines.

<u>Y</u>	<u>Z</u>	<u>R<sub>7</sub></u>	<u>K<sub>1</sub>-R<sub>6</sub></u>	<u>R<sub>10</sub></u>	<u>K<sub>2</sub>-R<sub>11</sub></u>	<u>R<sub>5</sub></u>	<u>R<sub>8</sub></u>
CH <sub>2</sub>	-	4-chloro-3-ethylphenoxy	C-H	OCF <sub>2</sub> CF <sub>2</sub> H	C-H	H	H
CH <sub>2</sub>	-	4-chloro-3-ethylphenoxy	N	OCF <sub>2</sub> CF <sub>2</sub> H	C-H	H	H
CH <sub>2</sub>	-	4-chloro-3-ethylphenoxy	C-H	OCF <sub>2</sub> CF <sub>2</sub> H	N	H	H
CH <sub>2</sub>	-	phenoxy	C-H	OCF <sub>2</sub> CF <sub>2</sub> H	C-H	H	H
CH <sub>2</sub>	-	phenoxy	N	OCF <sub>2</sub> CF <sub>2</sub> H	C-H	H	H
CH <sub>2</sub>	-	phenoxy	C-H	OCF <sub>2</sub> CF <sub>2</sub> H	N	H	H
CH <sub>2</sub>	-	4-chloro-3-ethylphenoxy	C-H	CF <sub>2</sub> CF <sub>3</sub>	C-H	H	H
CH <sub>2</sub>	-	4-chloro-3-ethylphenoxy	N	CF <sub>2</sub> CF <sub>3</sub>	C-H	H	H
CH <sub>2</sub>	-	4-chloro-3-ethylphenoxy	C-H	CF <sub>2</sub> CF <sub>3</sub>	N	H	H
CH <sub>2</sub>	-	phenoxy	C-H	CF <sub>2</sub> CF <sub>3</sub>	C-H	H	H
CH <sub>2</sub>	-	phenoxy	N	CF <sub>2</sub> CF <sub>3</sub>	C-H	H	H
CH <sub>2</sub>	-	phenoxy	C-H	CF <sub>2</sub> CF <sub>3</sub>	N	H	H

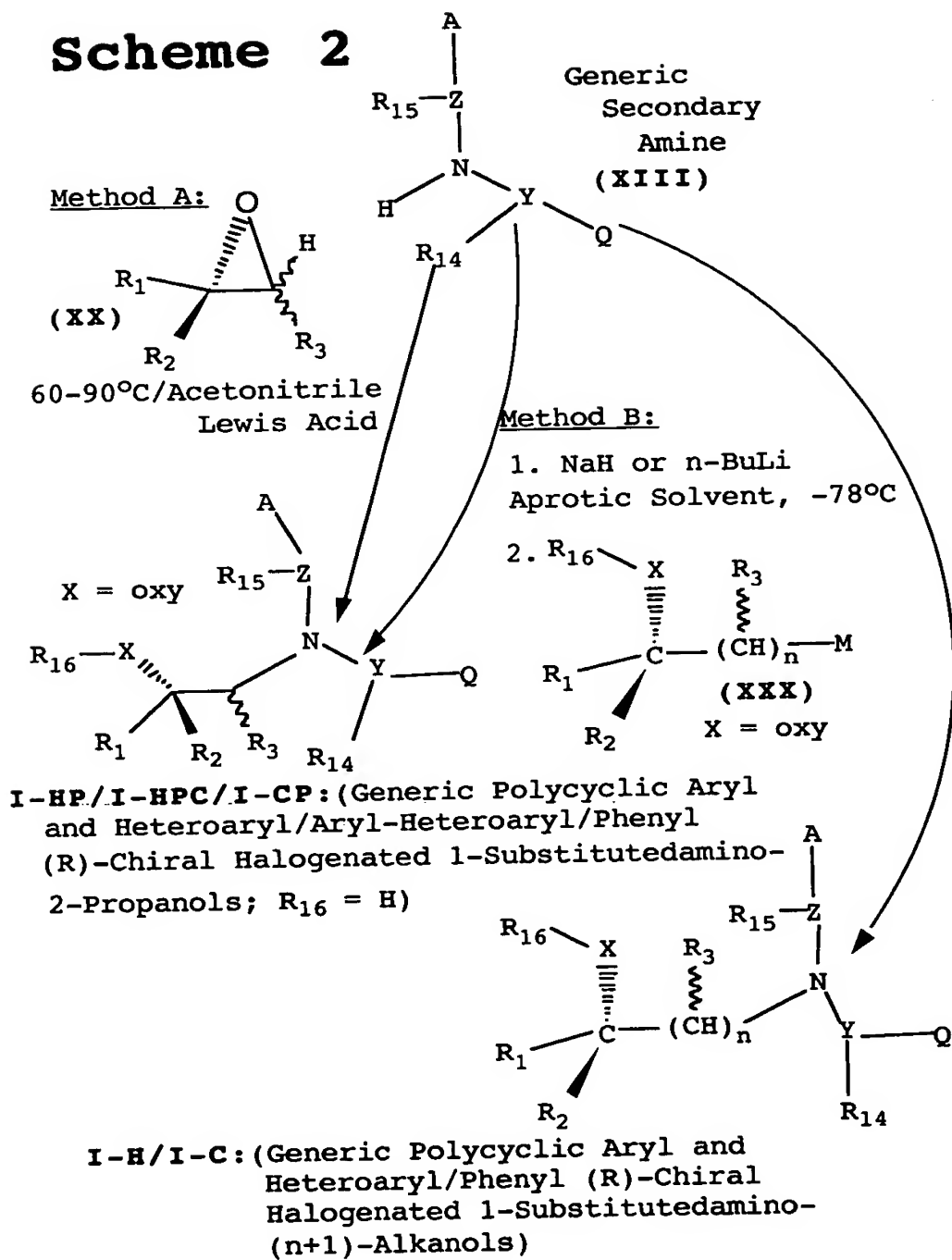
Table 8. (cont.) Structure of Substituted Tricyclic *tertiary*-2-oxyalkylamines.

<u>Y</u>	<u>Z</u>	<u>R<sub>7</sub></u>	<u>K<sub>1</sub>-R<sub>6</sub></u>	<u>R<sub>10</sub></u>	<u>K<sub>2</sub>- R<sub>11</sub></u>	<u>R<sub>5</sub></u>	<u>R<sub>8</sub></u>
CH <sub>2</sub>	-	4-chloro-3-ethylphenoxy	C-H	CF <sub>3</sub>	C-H	H	H
CH <sub>2</sub>	-	4-chloro-3-ethylphenoxy	N	CF <sub>3</sub>	C-H	H	H
CH <sub>2</sub>	-	4-chloro-3-ethylphenoxy	C-H	CF <sub>3</sub>	N	H	H
CH <sub>2</sub>	-	phenoxy	C-H	CF <sub>3</sub>	C-H	H	H
CH <sub>2</sub>	-	phenoxy	N	CF <sub>3</sub>	C-H	H	H
CH <sub>2</sub>	-	phenoxy	C-H	CF <sub>3</sub>	N	H	H
CH <sub>2</sub>	-	4-chloro-3-ethylphenoxy	C-H	OCF <sub>2</sub> CF <sub>2</sub> H	C-H	H	F
CH <sub>2</sub>	-	4-chloro-3-ethylphenoxy	N	OCF <sub>2</sub> CF <sub>2</sub> H	C-H	H	F
CH <sub>2</sub>	-	4-chloro-3-ethylphenoxy	C-H	OCF <sub>2</sub> CF <sub>2</sub> H	N	H	F
CH <sub>2</sub>	-	4-chloro-3-ethylphenoxy	C-H	2-furyl	C-H	H	H
CH <sub>2</sub>	-	4-chloro-3-ethylphenoxy	N	2-furyl	C-H	H	H
CH <sub>2</sub>	-	4-chloro-3-ethylphenoxy	C-H	2-furyl	N	H	H
CH <sub>2</sub>	-	4-chloro-3-ethylphenoxy	C-H	SCF <sub>3</sub>	C-H	H	H
CH <sub>2</sub>	-	4-chloro-3-ethylphenoxy	N	SCF <sub>3</sub>	C-H	H	H
CH <sub>2</sub>	-	4-chloro-3-ethylphenoxy	C-H	SCF <sub>3</sub>	N	H	H

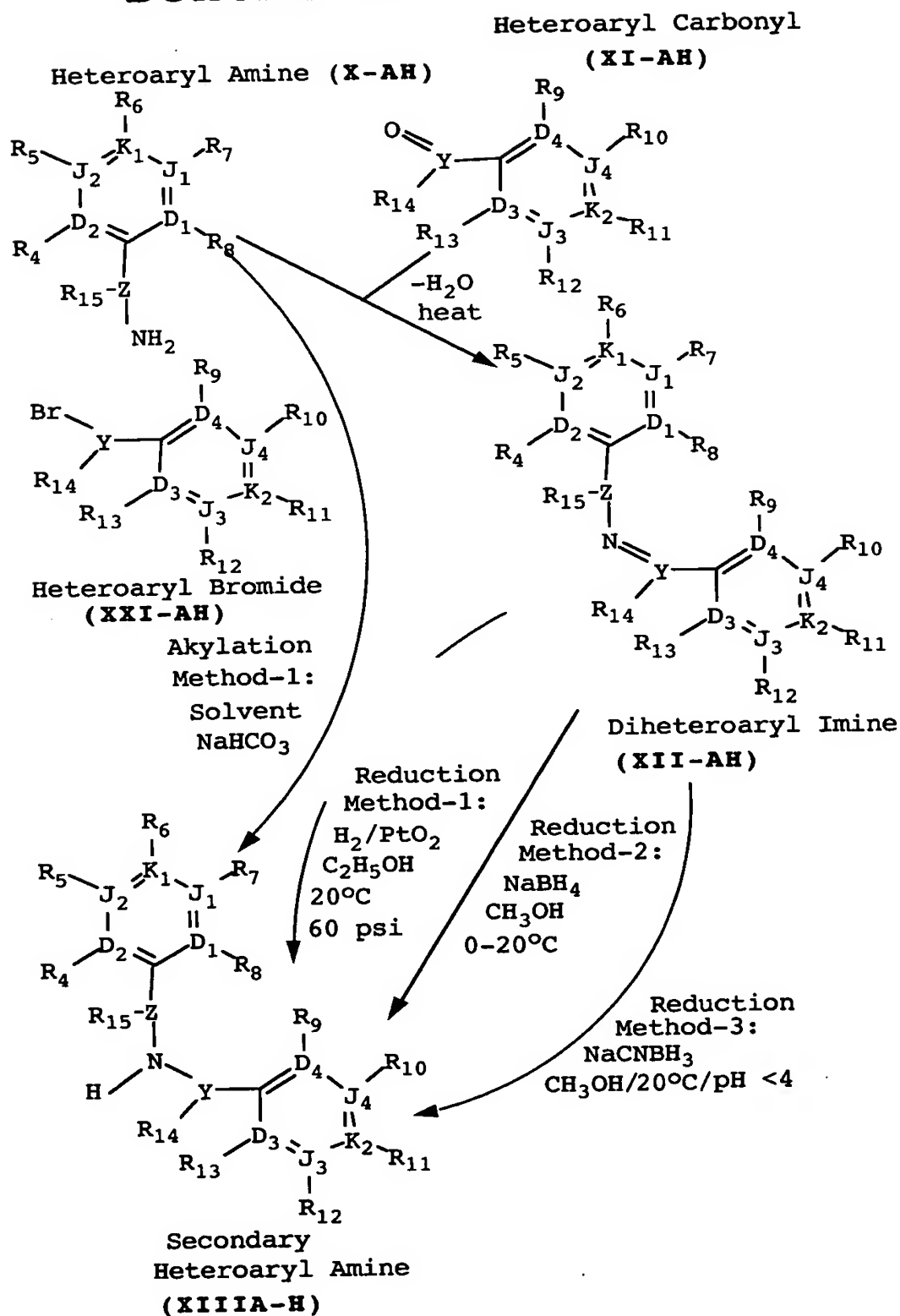
## Scheme 1



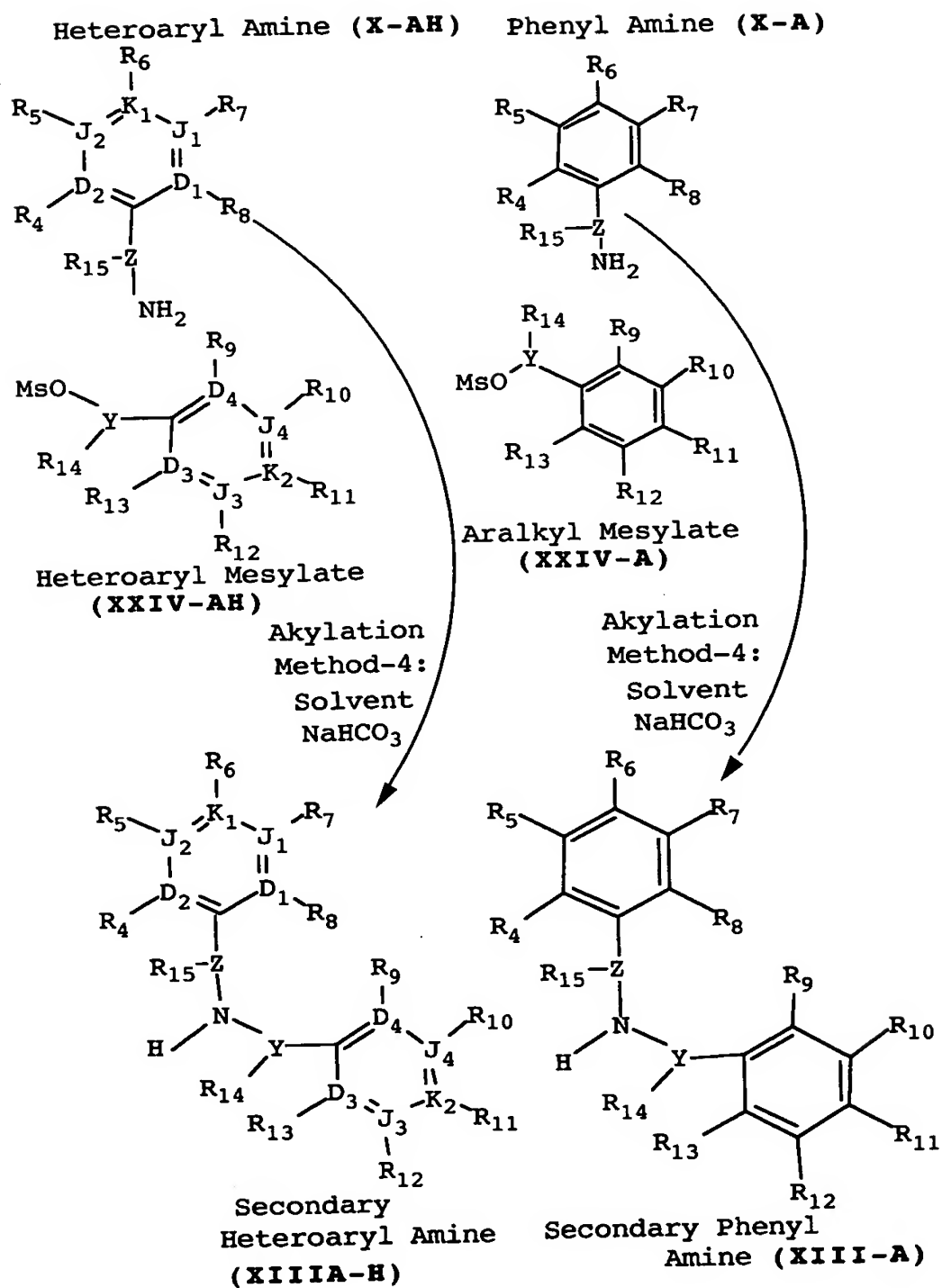
# Scheme 2



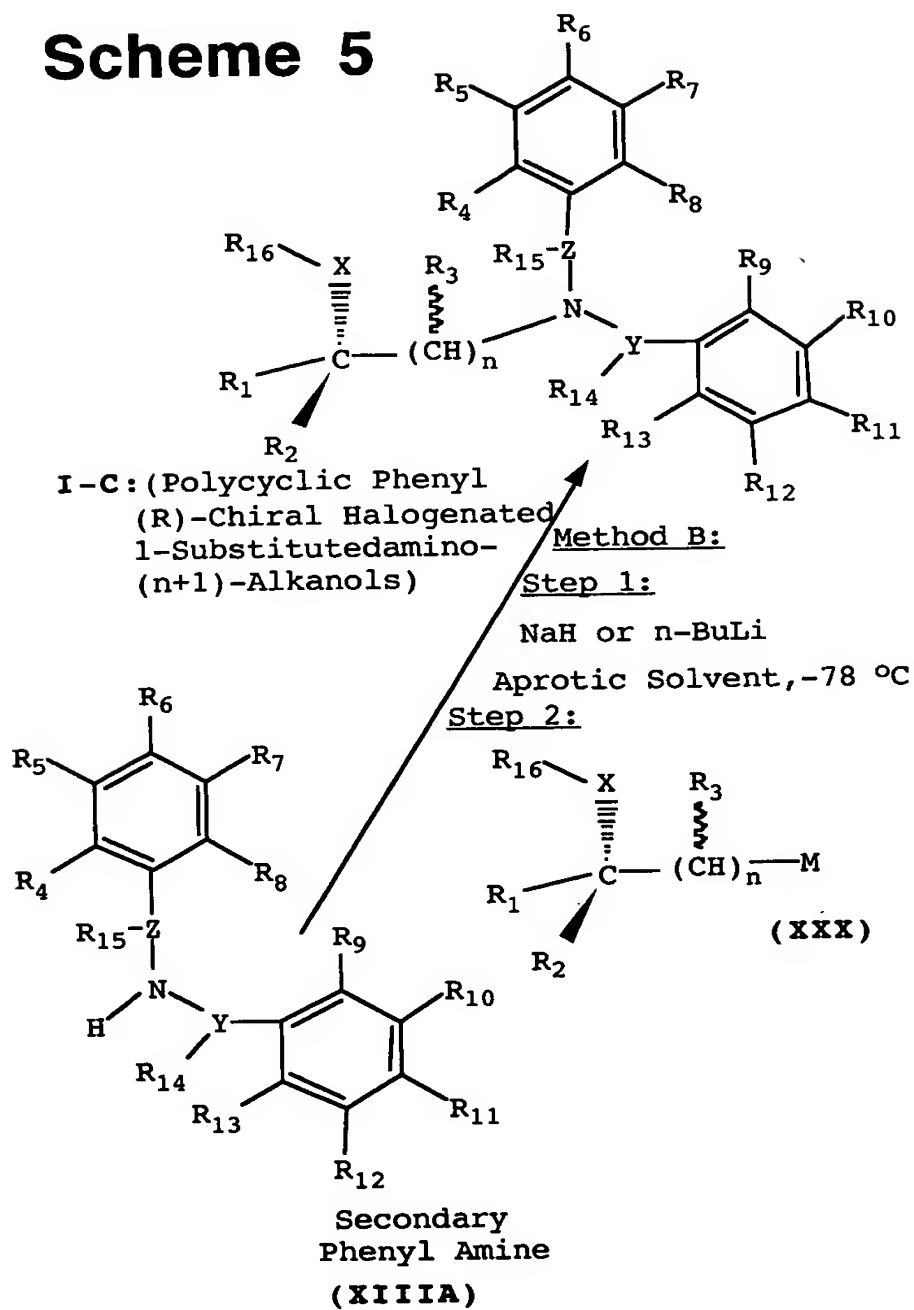
# Scheme 3



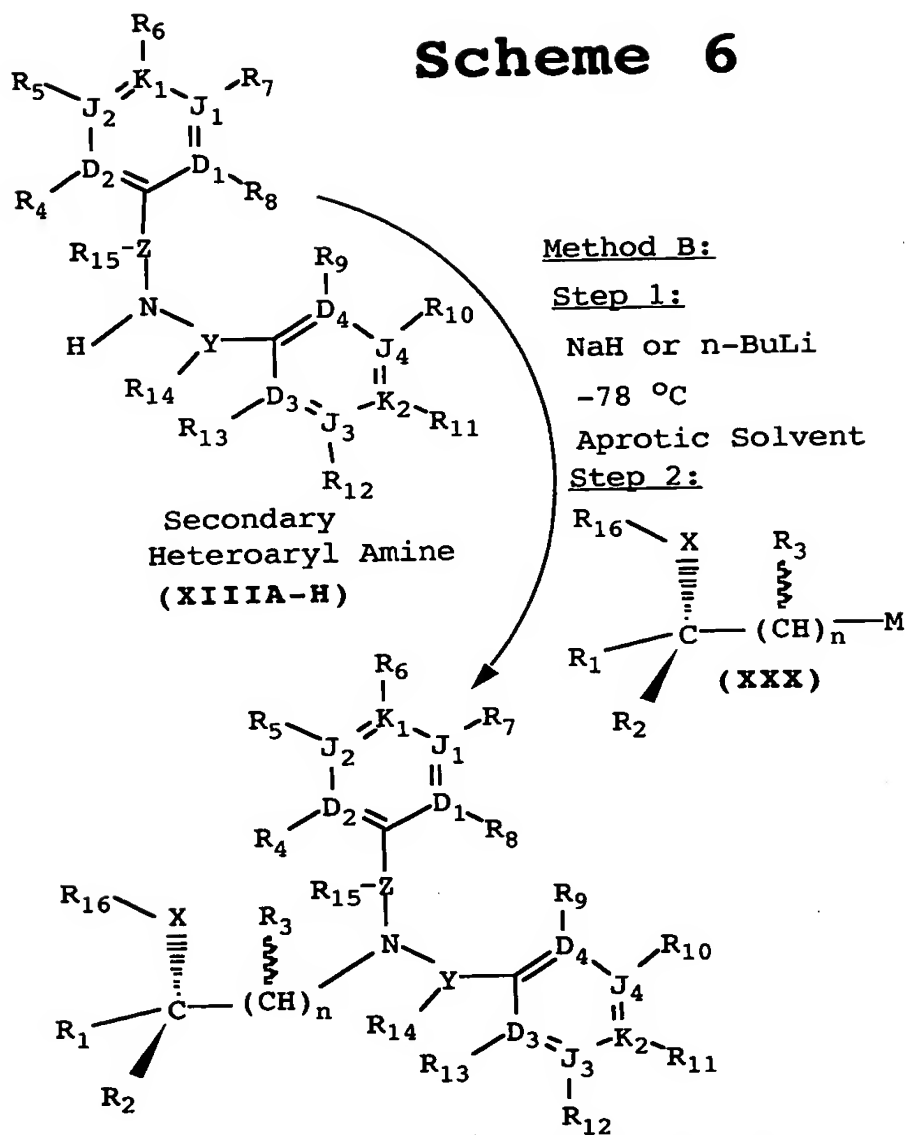
# Scheme 4



# Scheme 5



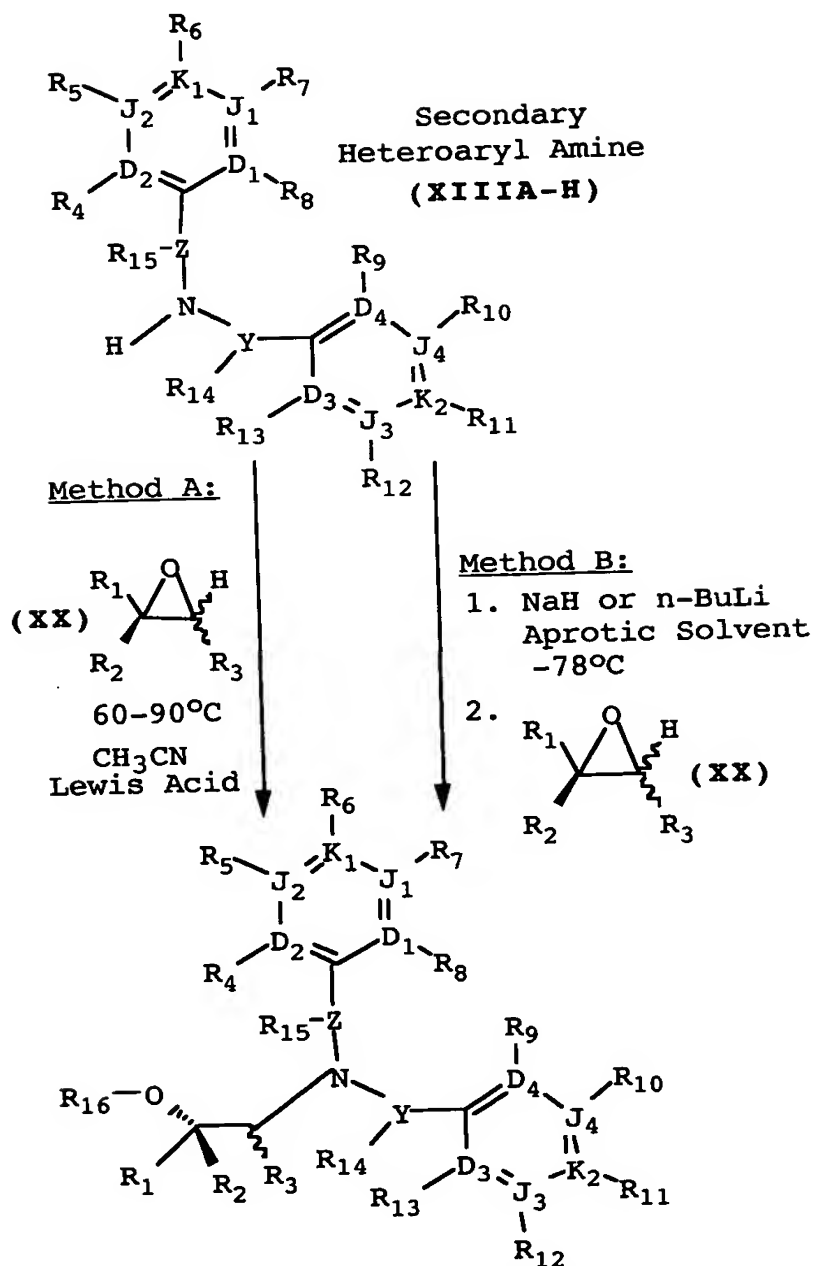
## Scheme 6



**I-H/I-C:** (Generic Polycyclic Aryl and Heteroaryl/Phenyl (R)-Chiral Halogenated 1-Substitutedamino-(n+1)-Alkanols; X = oxy)



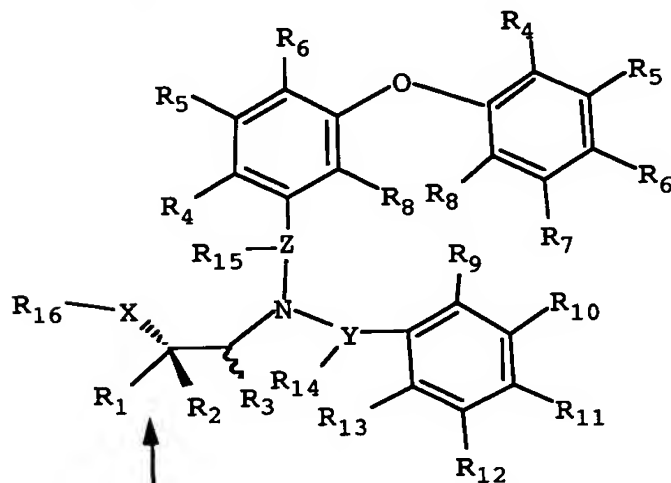
## Scheme 7



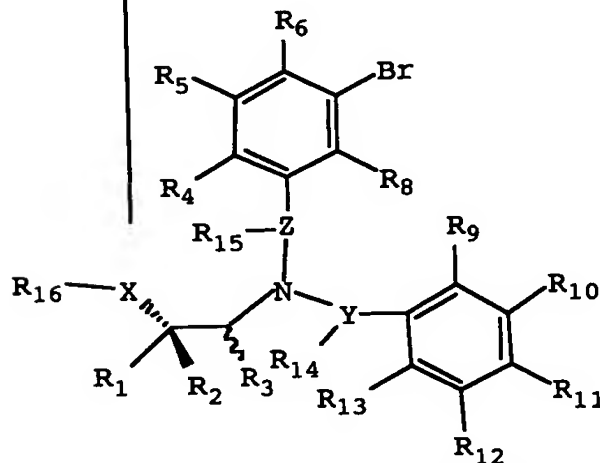
**I-HP/I-HPC:** (Generic Polycyclic Aryl and Heteroaryl/Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols;  $R_{16} = \text{H}$ )

## Scheme 8

**I-CP:** (Polycyclic 3-Phenoxyphenyl (R)-Chiral  
Halogenated 1-Substitutedamino-2-Propanols;  
 $R_{16} = H$ ;  $X = \text{oxy}$ )

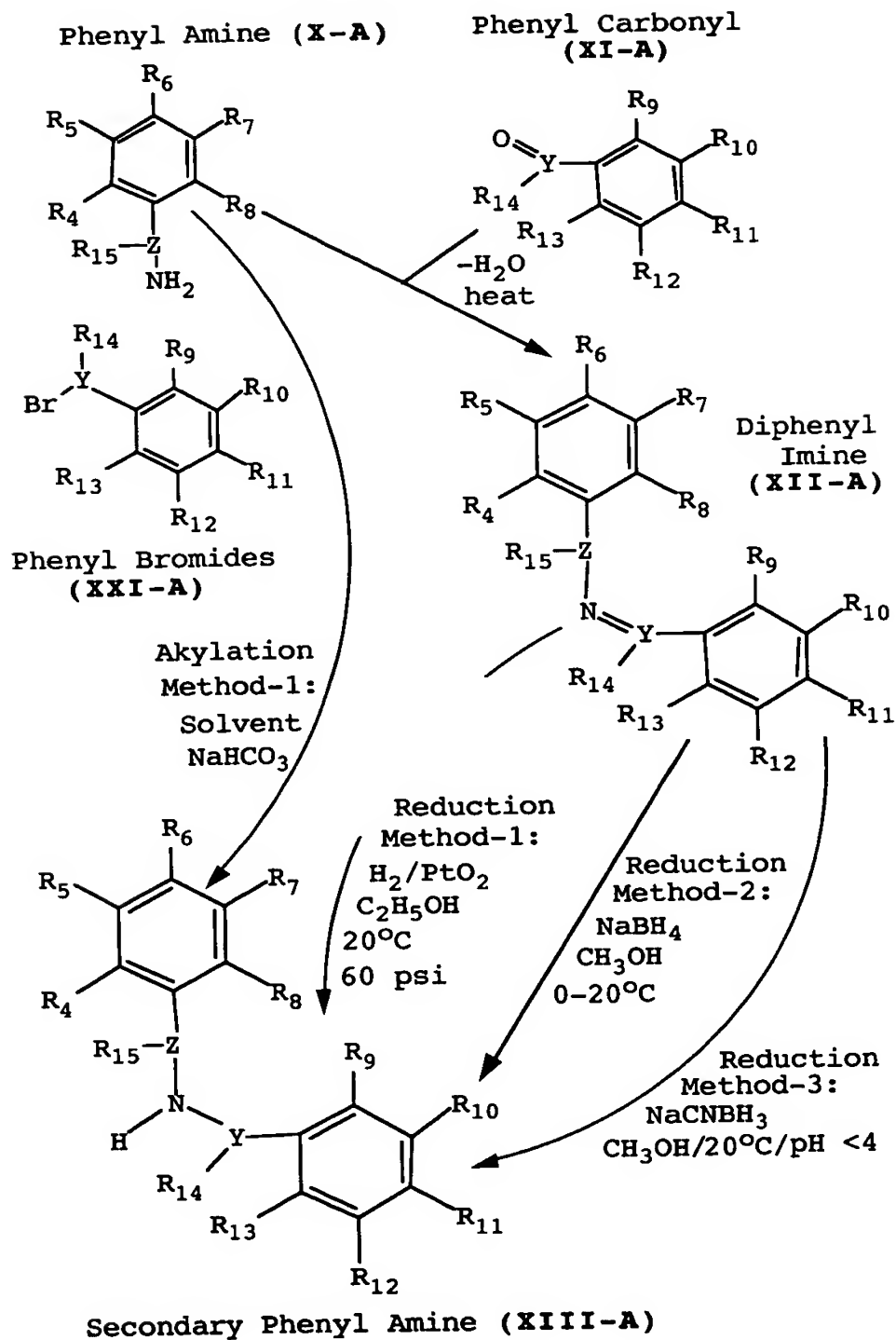


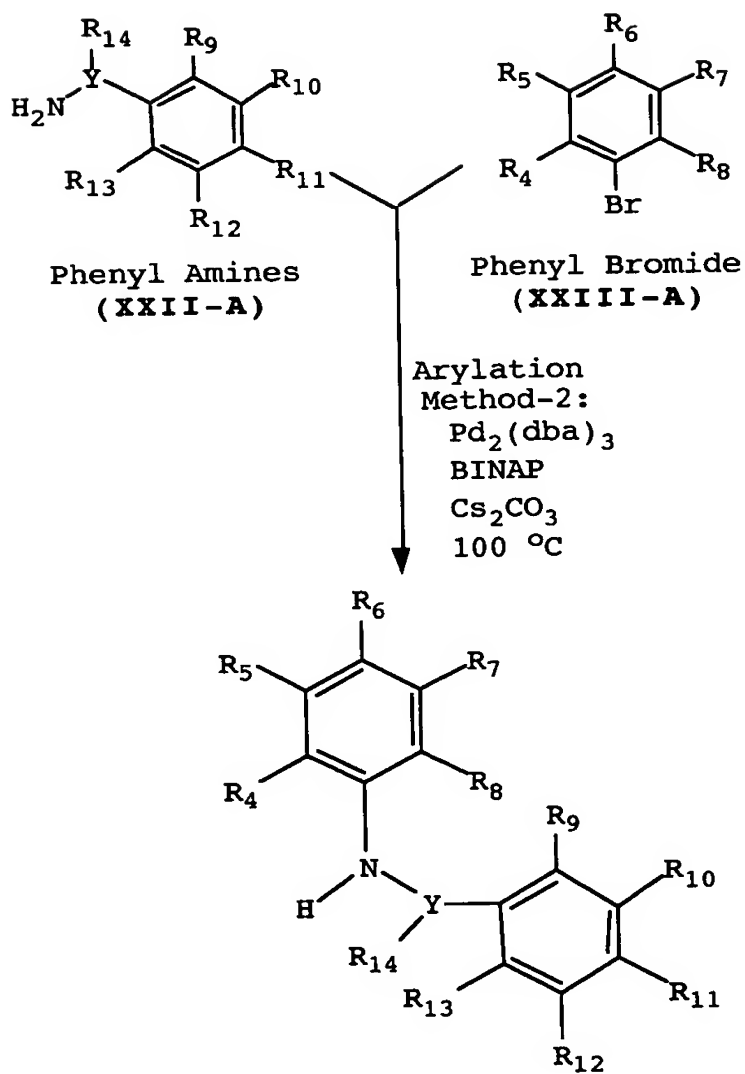
$\text{Cu}_2(\text{triflate})_2 \cdot \text{Benzene}$   
2 equivalents of a phenol  
2.5 equiv.  $\text{Cs}_2\text{CO}_3$   
2.5 equiv. 1-Naphthoic Acid  
4A Molecular Sieves  
Dimethylacetamide/toluene  
105 °C/10-14 Days



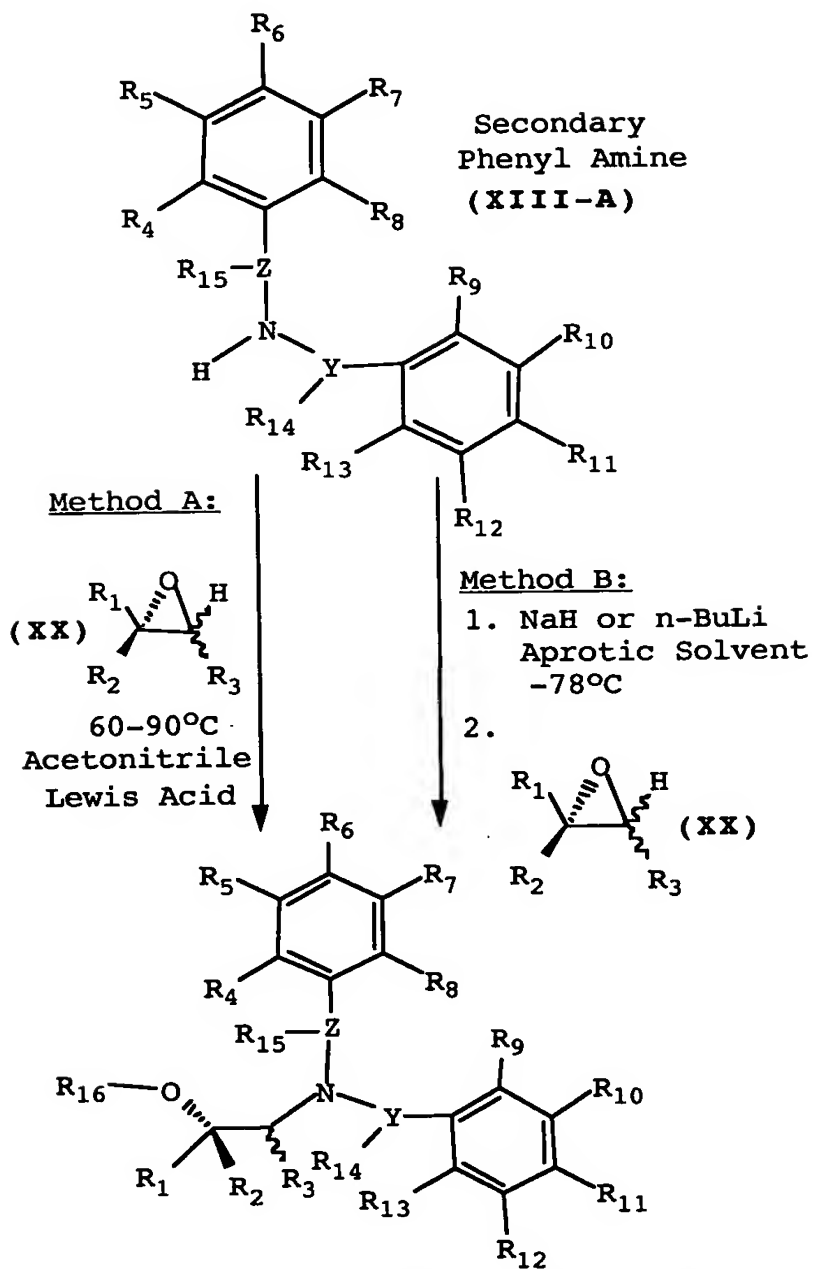
**I-CP:** (Polycyclic 3-Bromophenyl (R)-Chiral  
Halogenated 1-Substitutedamino-  
2-Propanols;  $R_{16} = H$ ;  $X = \text{oxy}$ )

# Scheme 9



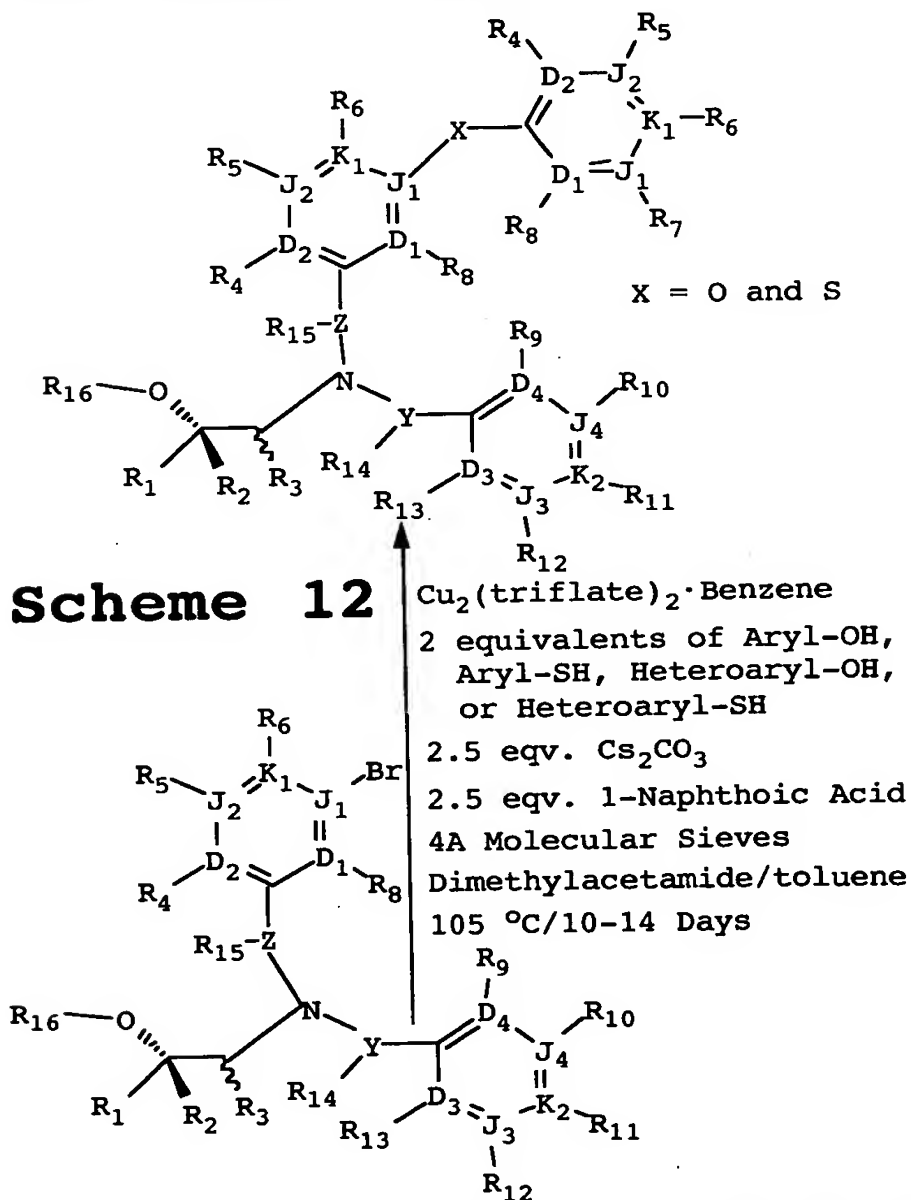
**Scheme 10****Secondary Phenyl Amine (XIII-A)**

# Scheme 11



**I-CP:** (Polycyclic Phenyl (R)-Chiral  
 Halogenated 1-Substitutedamino-  
 2-Propanol;  $R_{16} = H$ )

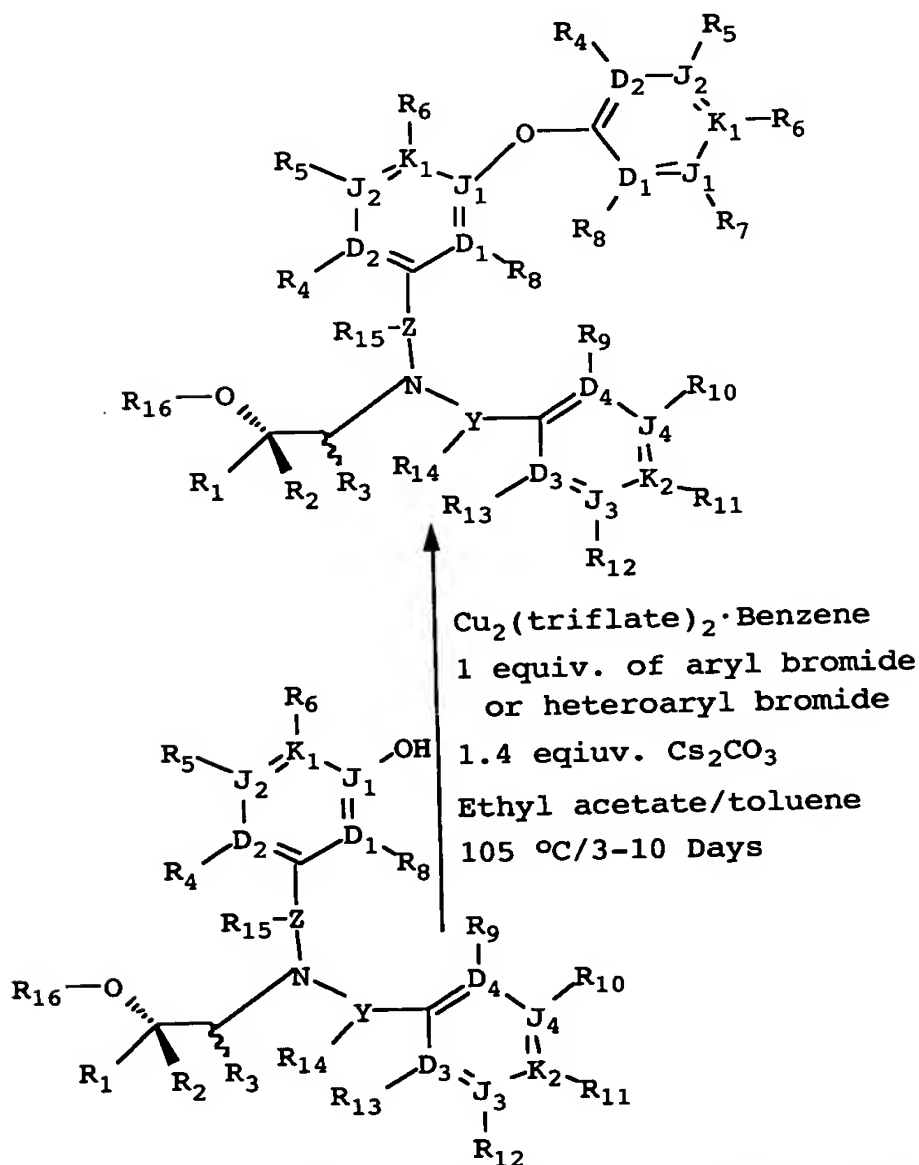
**I-HP/I-HPC:** (Generic Polycyclic 3-Aryloxyaryl, 3-Heteroaryloxyaryl, 3-Heteroaryloxyheteroaryl, 3-Aryloxyheteroaryl, 3-Arylthioaryl, 3-Heteroarylthioaryl, 3-Heteroarylthioheteroaryl, 3-Arylthioheteroaryl Aryl and Heteroaryl/Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols)



**I-HP/I-HPC:** (Generic Polycyclic 3-Bromo Aryl and Heteroaryl/Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols)

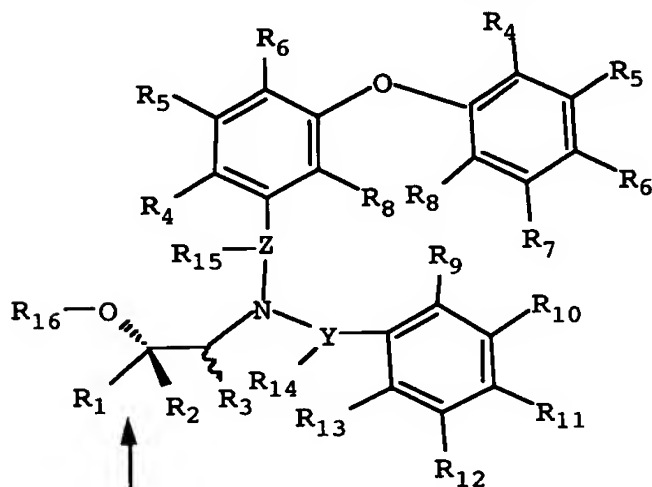
# Scheme 13

**I-HP/I-HPC:** (Generic Polycyclic 3-Aryloxyaryl, 3-Heteroaryloxyaryl, 3-Aryloxyheteroaryl or 3-Heteroaryloxyheteroaryl Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols)



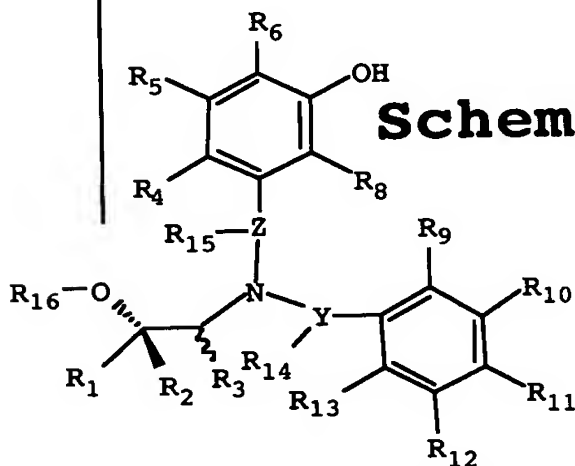
**I-HP/I-HPC:** (Generic Polycyclic 3-Hydroxy Aryl and Heteroaryl/Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols)

**I-CP: (Generic Substituted Polycyclic  
3-Phenoxyphenyl Aryl (R)-Chiral Halogenated  
1-Substitutedamino-2-Propanols)**



$\text{Cu}_2(\text{triflate})_2 \cdot \text{Benzene}$   
 1 equiv. of aryl bromide  
 or heteroaryl bromide  
 1.4 equiv.  $\text{Cs}_2\text{CO}_3$   
 Ethyl acetate/toluene  
 105 °C/3-10 Days

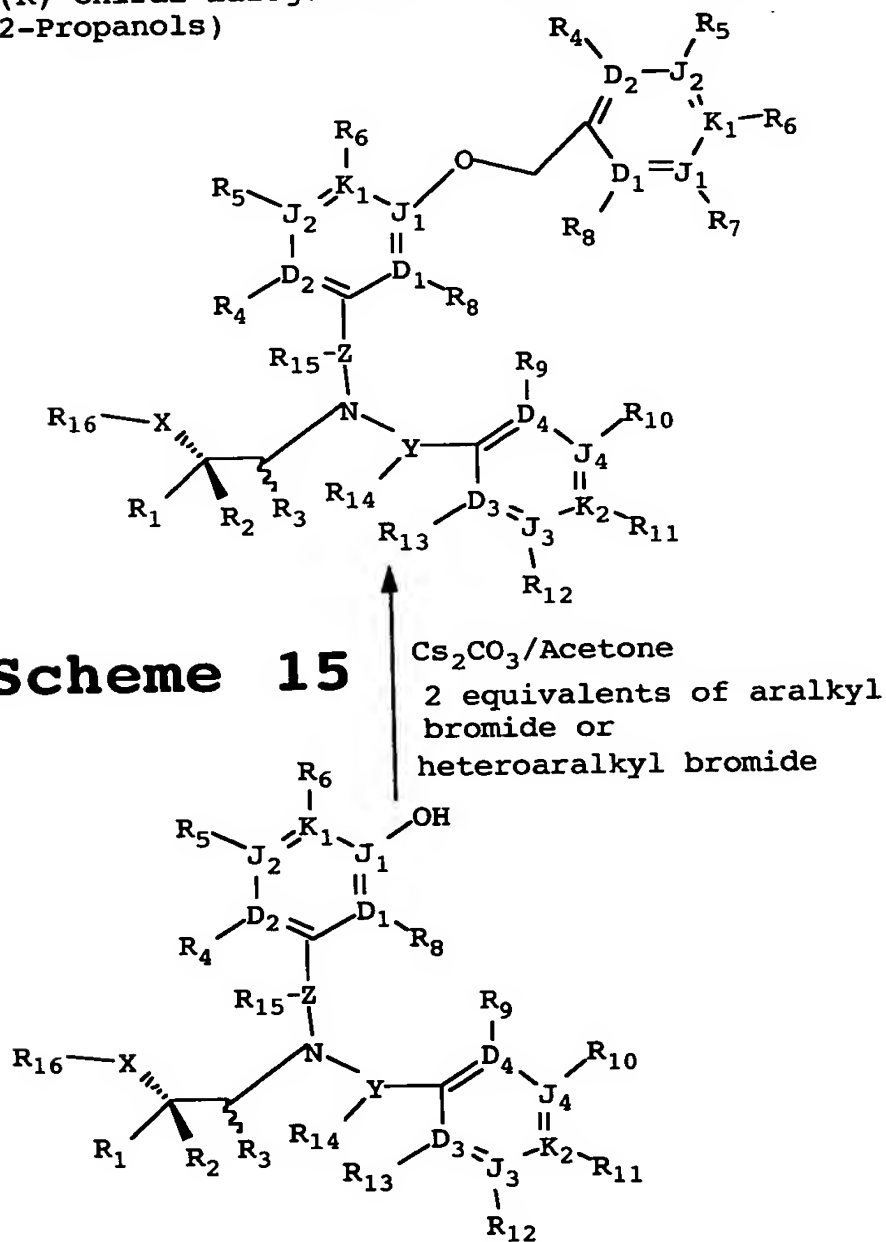
**Scheme 14**



**I-CP: (Generic Polycyclic 3-Hydroxyphenyl  
Aryl (R)-Chiral Halogenated  
1-Substitutedamino-2-Propanols)**



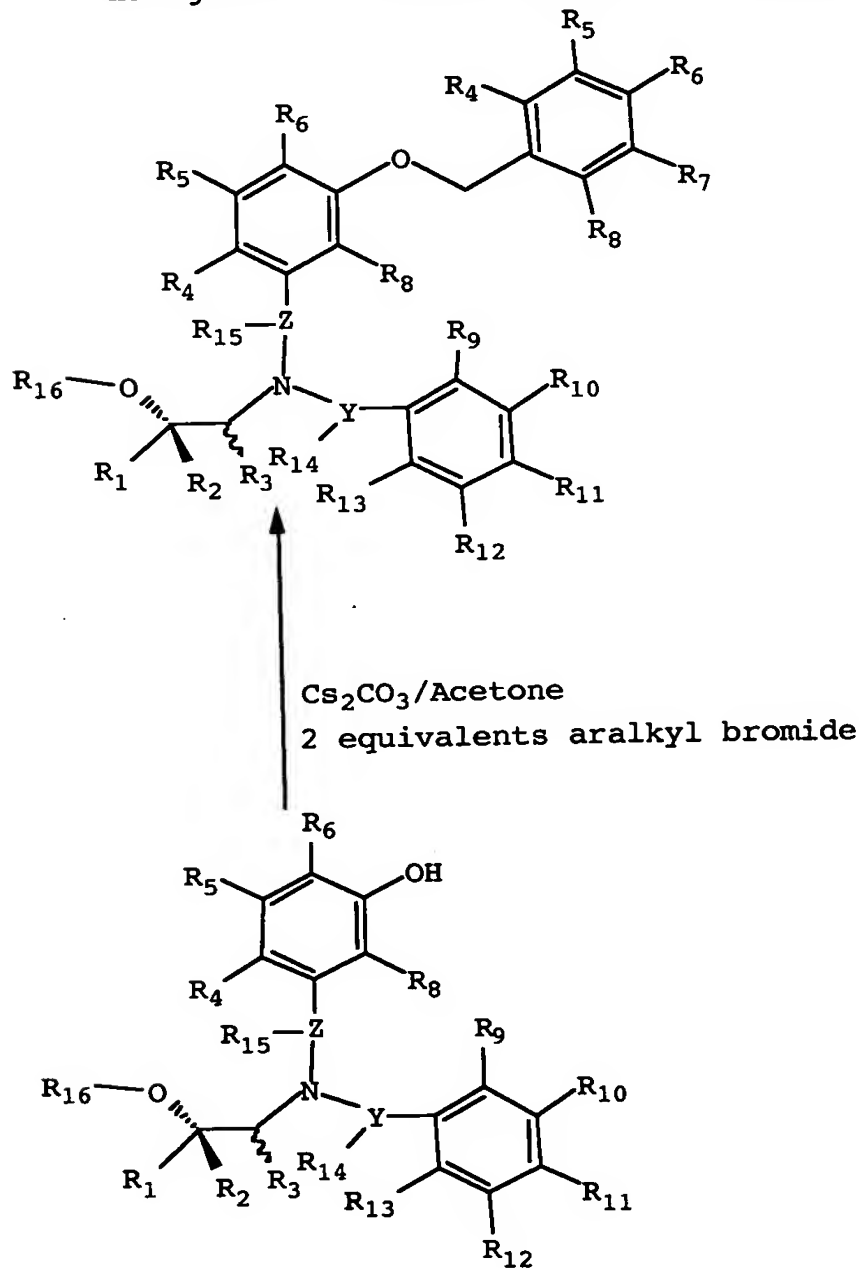
**I-HP/I-HPC:** (Generic Polycyclic 3-Aralkyloxyaryl, 3-Heteraralkyloxyaryl, 3-Aralkyloxyheteroaryl, or 3-Heteraralkyloxyheteroaryl Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols)



**I-HP/I-HPC:** (Generic Polycyclic 3-Hydroxy Aryl and Heteroaryl/Aryl-Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols)

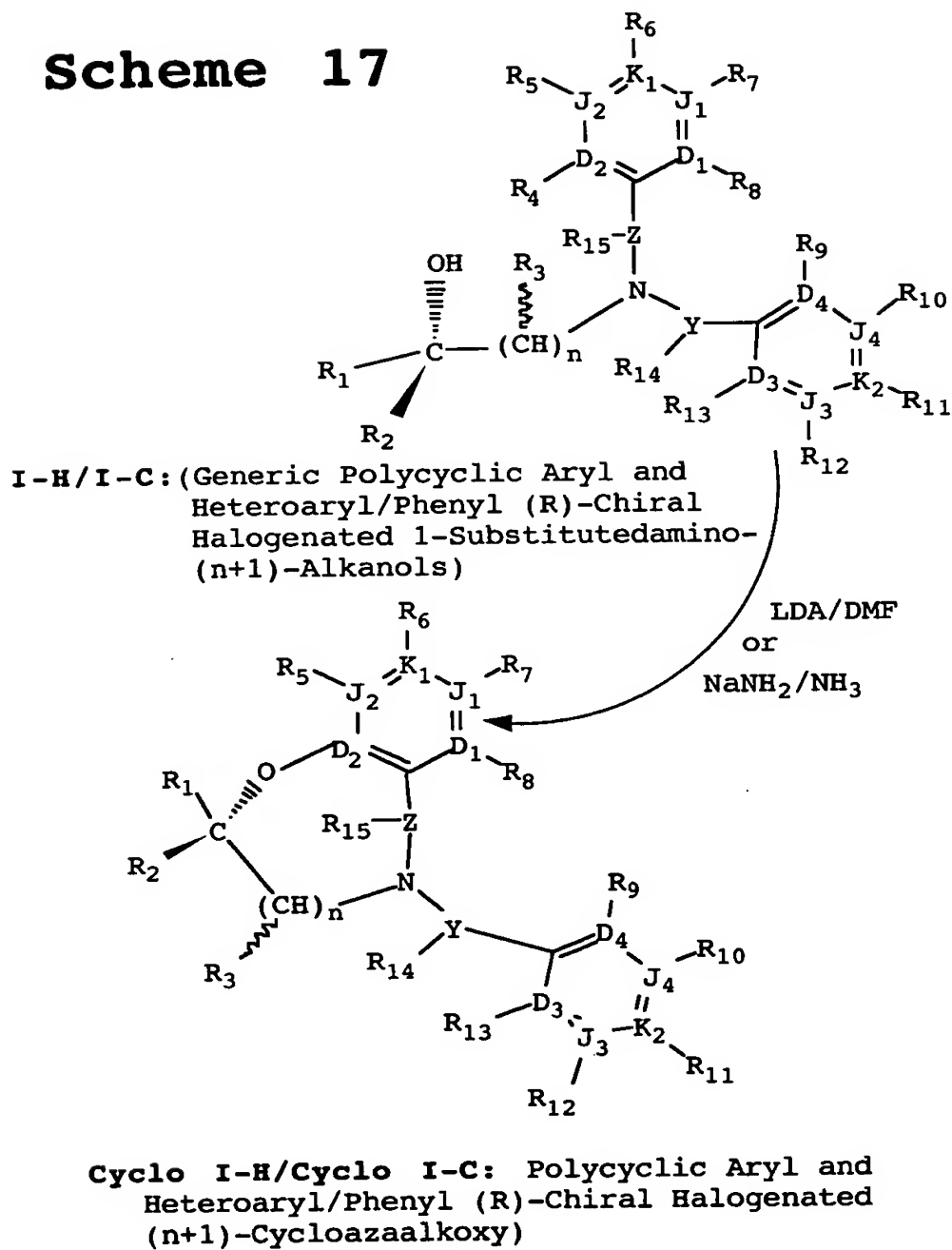
## Scheme 16

**I-CP:**(Polycyclic 3-Aralkyloxyaryl Phenyl (R)-Chiral  
Halogenated 1-Substitutedamino-2-Propanols)

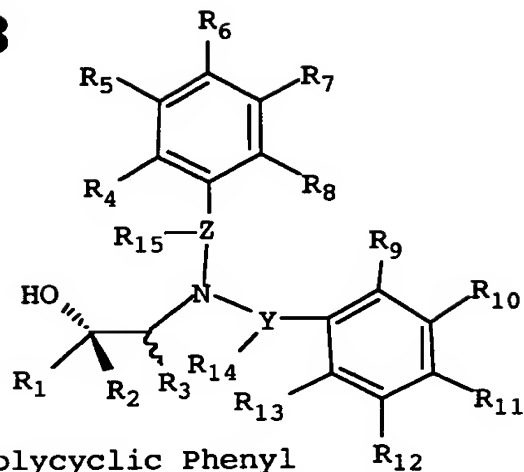


**I-CP:**(Polycyclic 3-Hydroxyphenyl Phenyl (R)-Chiral  
Halogenated 1-Substitutedamino-2-Propanols)

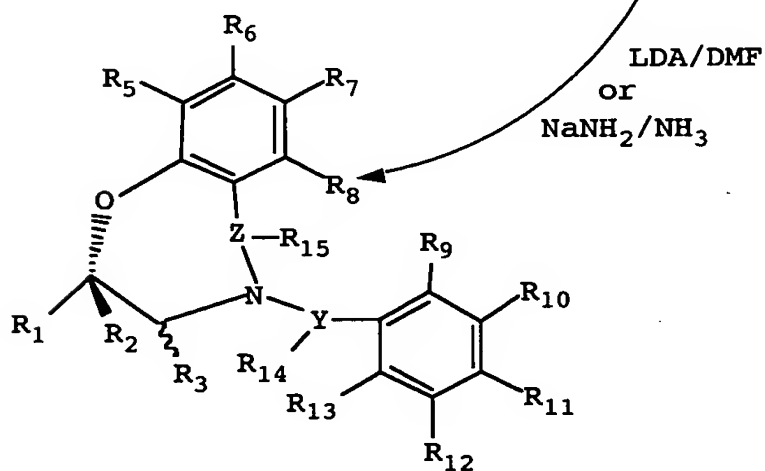
# Scheme 17



# Scheme 18



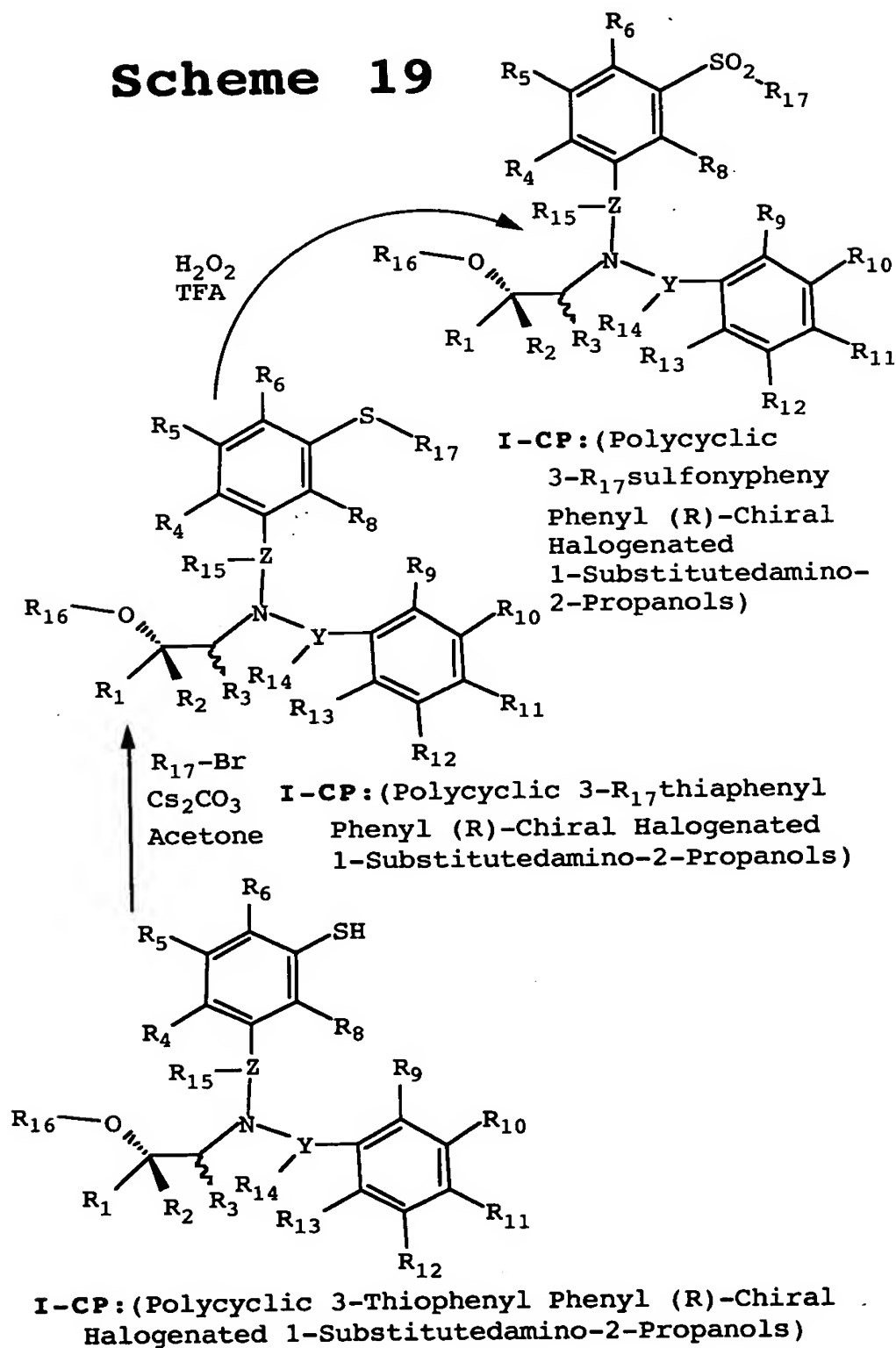
**I-CP:** (Generic Polycyclic Phenyl  
Phenyl (R)-Chiral Halogenated  
1-Substitutedamino-2-Propanols)



LDA/DMF  
or  
NaNH<sub>2</sub>/NH<sub>3</sub>

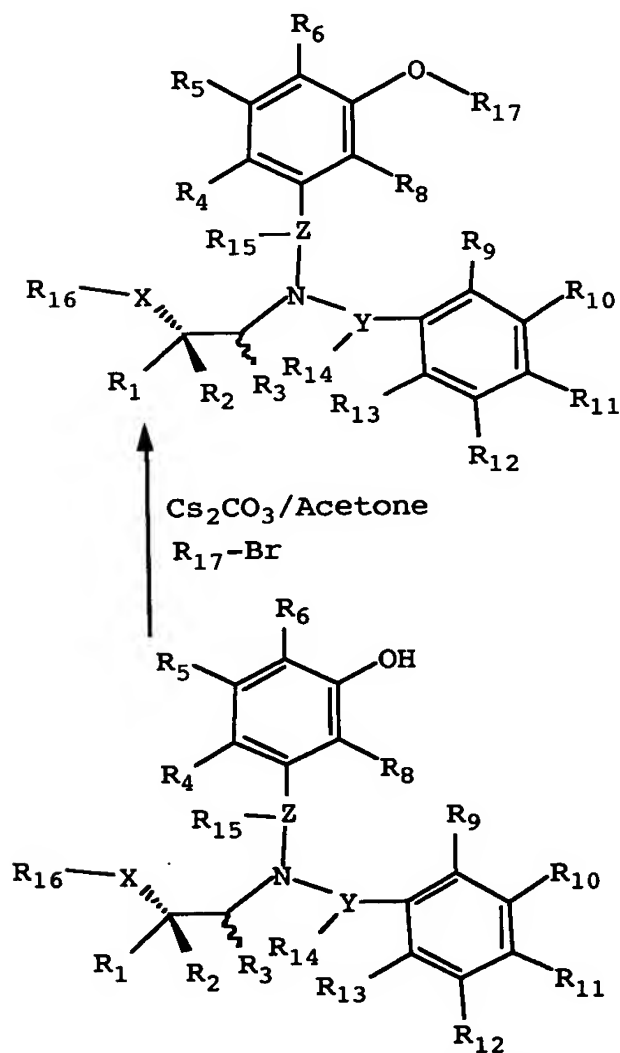
**Cyclo I-CP:** (Polycyclic Phenyl Phenyl  
(R)-Chiral Halogenated  
Cycloazaalkoxy)

## Scheme 19



## Scheme 20

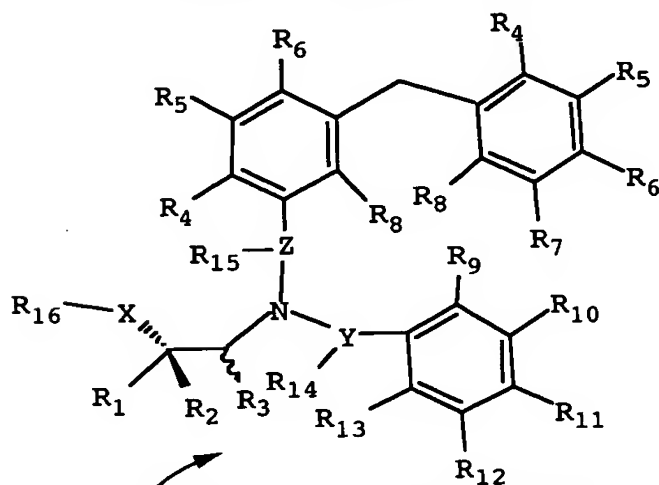
**I-CP:**(Polycyclic 3- R<sub>17</sub>-oxyphenyl  
Phenyl (R)-Chiral Halogenated  
1-Substitutedamino-2-Propanols)



**I-CP:**(Polycyclic 3-Hydroxyphenyl  
Phenyl (R)-Chiral Halogenated  
1-Substitutedamino-2-Propanols)

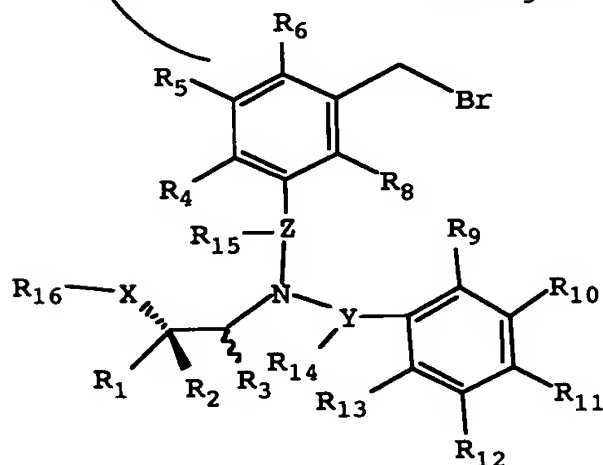
## Scheme 21

**I-CP:** (Polycyclic 3-Arylmethylphenyl  
Phenyl (R)-Chiral Halogenated  
1-Substitutedamino-2-Propanols)



$\text{Pd}(\text{triphenylphosphine})_4$   
Aryl-B(OH)<sub>2</sub>  
Toluene  
2 M Na<sub>2</sub>CO<sub>3</sub>  
Ethanol

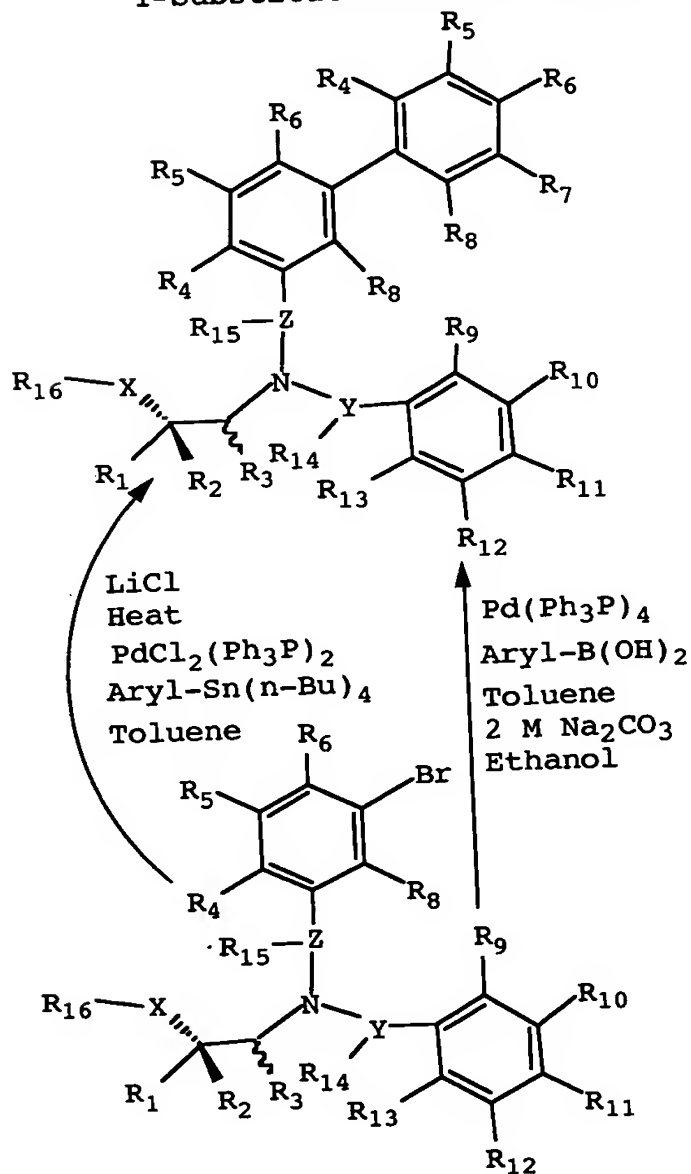
**NOTE:** Use of  
Heteroaryl-B(OH)<sub>2</sub> will  
give the heteroarylmethyl  
analog of I-CP.



**I-CP:** (Polycyclic 3-Bromomethylphenyl  
Phenyl (R)-Chiral Halogenated  
1-Substitutedamino-2-Propanols)

## Scheme 22

**I-CP:** (Polycyclic 3-Arylphenyl  
Phenyl (R)-Chiral Halogenated  
1-Substitutedamino-2-Propanols)

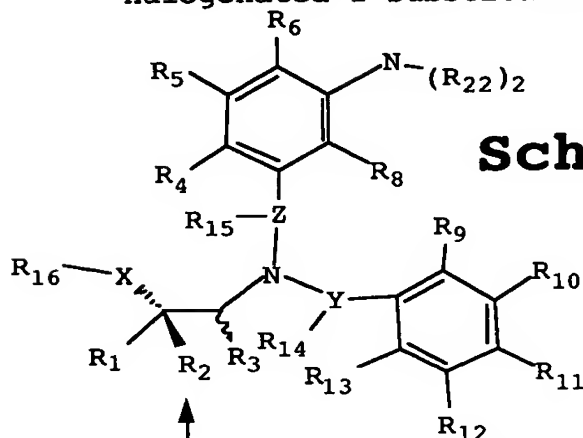


**I-CP:** (Polycyclic 3-Bromophenyl  
Phenyl (R)-Chiral Halogenated  
1-Substitutedamino-2-Propanols)

**NOTE:** Use of Heteroaryl-B(OH)<sub>2</sub> will give  
the heteroarylmethyl analog of I-CP.

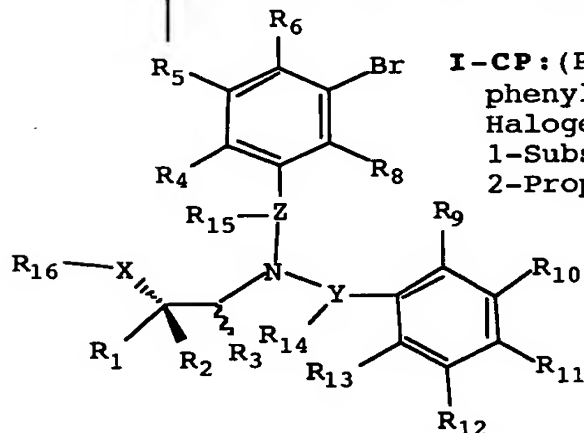


**I-CP:** (Polycyclic 3- $R_{22}$ -aminophenyl Phenyl (R)-Chiral  
Halogenated 1-Substitutedamino-2-Propanols)



## Scheme 23

$R_{22}$ -primary or secondary amine  
Pd(dba)<sub>3</sub>/R-(+)-BINAP  
2.5 equiv. Cs<sub>2</sub>CO<sub>3</sub>  
Toluene/100 °C/1-2 Days

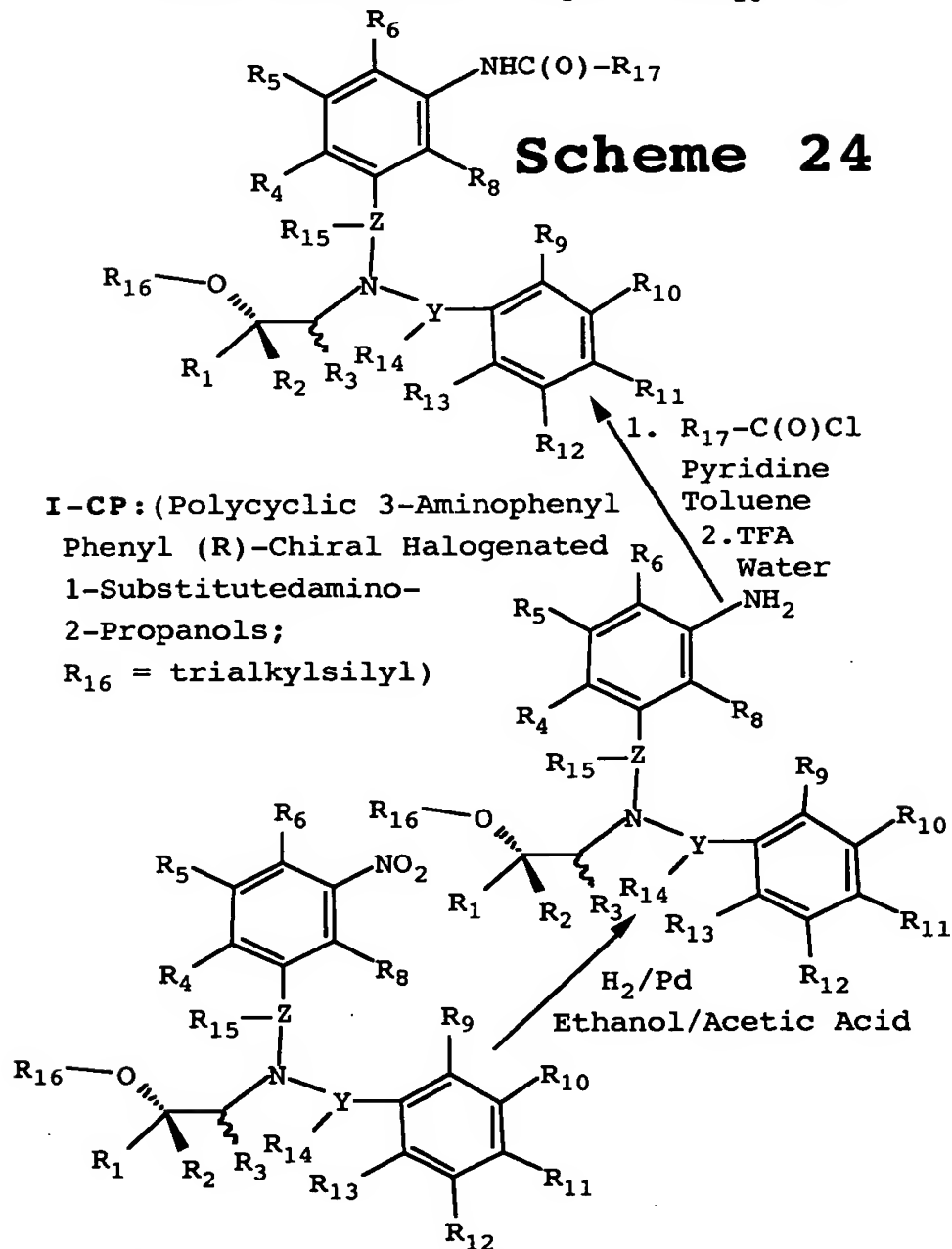


**I-CP:** (Polycyclic 3-Bromo-  
phenyl Phenyl (R)-Chiral  
Halogenated  
1-Substitutedamino-  
2-Propanols)

$R_{22}$  is selected independently from any one or two of the following groups: hydrido, hydroxy, aryloxy, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkoxy, halocycloalkoxyalkyl, arylsulfinylalkyl, arylsulfonylalkyl, alkylamino cycloalkylsulfinylalkyl, cycloalkylsulfonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, hydroxyalkyl, amino, alkoxy, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, heteroaryl, halocycloalkenyloxyalkyl, heteroarylalkyl, aryloxyalkyl, halocycloalkenyl, and heteroarylthioalkyl.

**I-CP:** (Polycyclic 3- $R_{17}$ -C(O)amidophenyl  
Phenyl (R)-Chiral Halogenated  
1-Substitutedamino-2-Propanols;  $R_{16} = H$ )

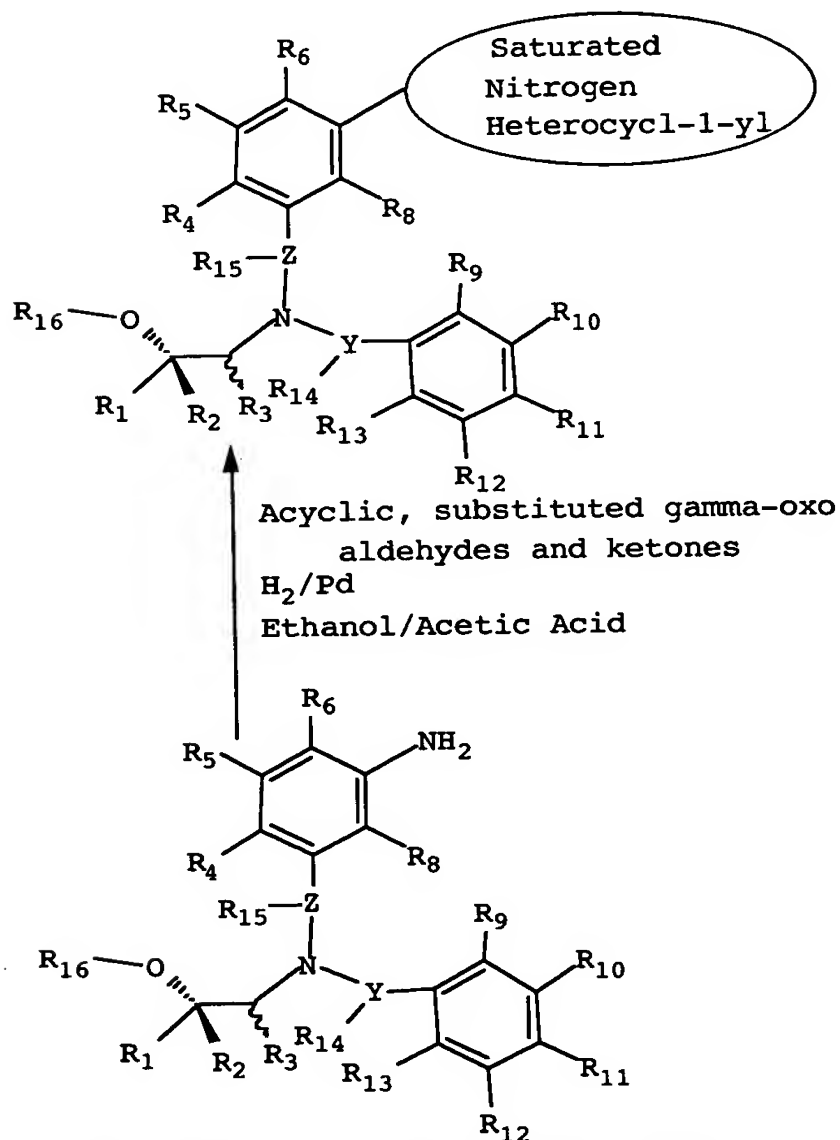
## Scheme 24



**I-CP:** (Polycyclic 3-Nitrophenyl Phenyl  
(R)-Chiral Halogenated 1-Substitutedamino-  
2-Propanols;  $R_{16} = \text{trialkylsilyl}$ )

## Scheme 25

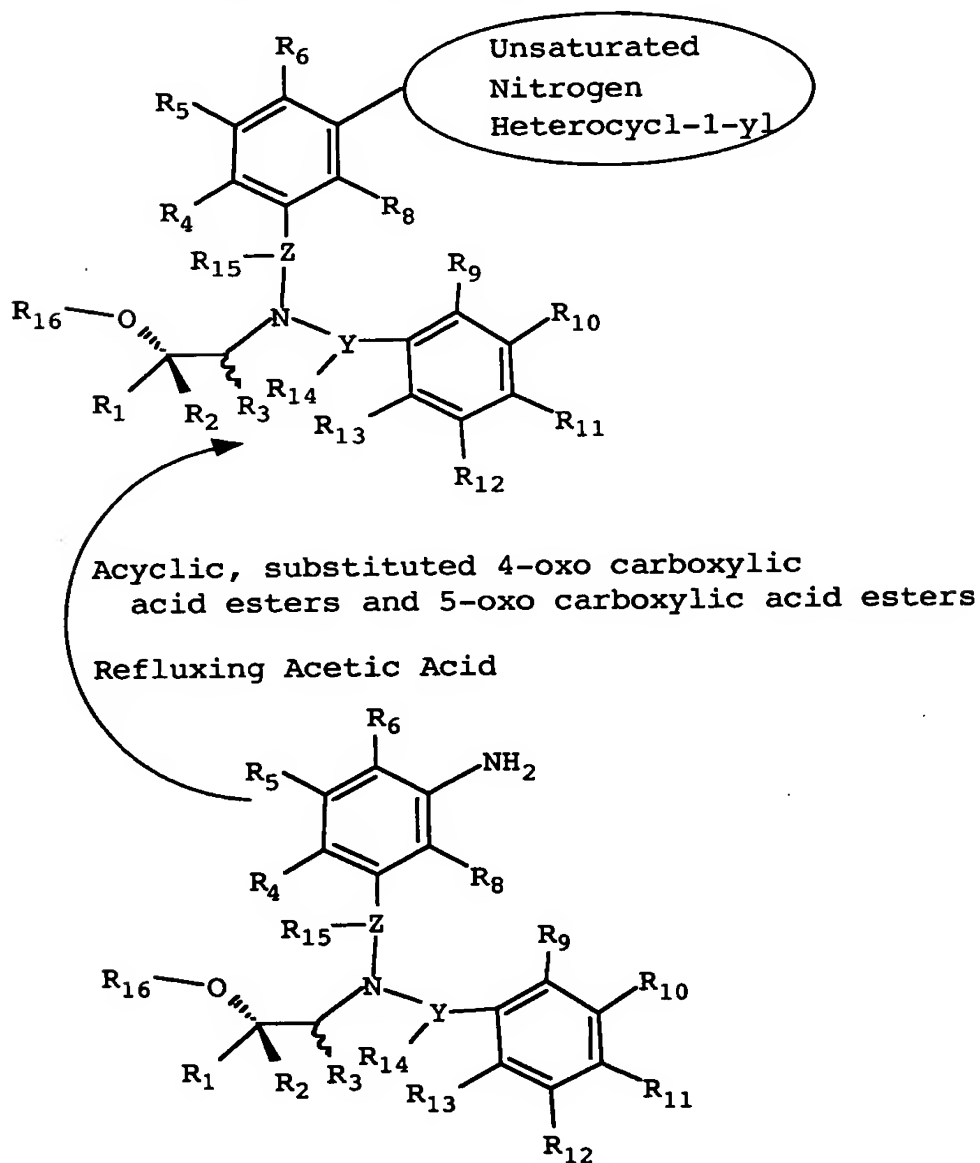
**I-CP:** (Polycyclic 3-(Saturated nitrogen heterocycl-1-yl)phenyl Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols;  $R_{16} = H$ )



**I-CP:** (Polycyclic 3-Aminophenyl Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols;  $R_{16} = H$ )

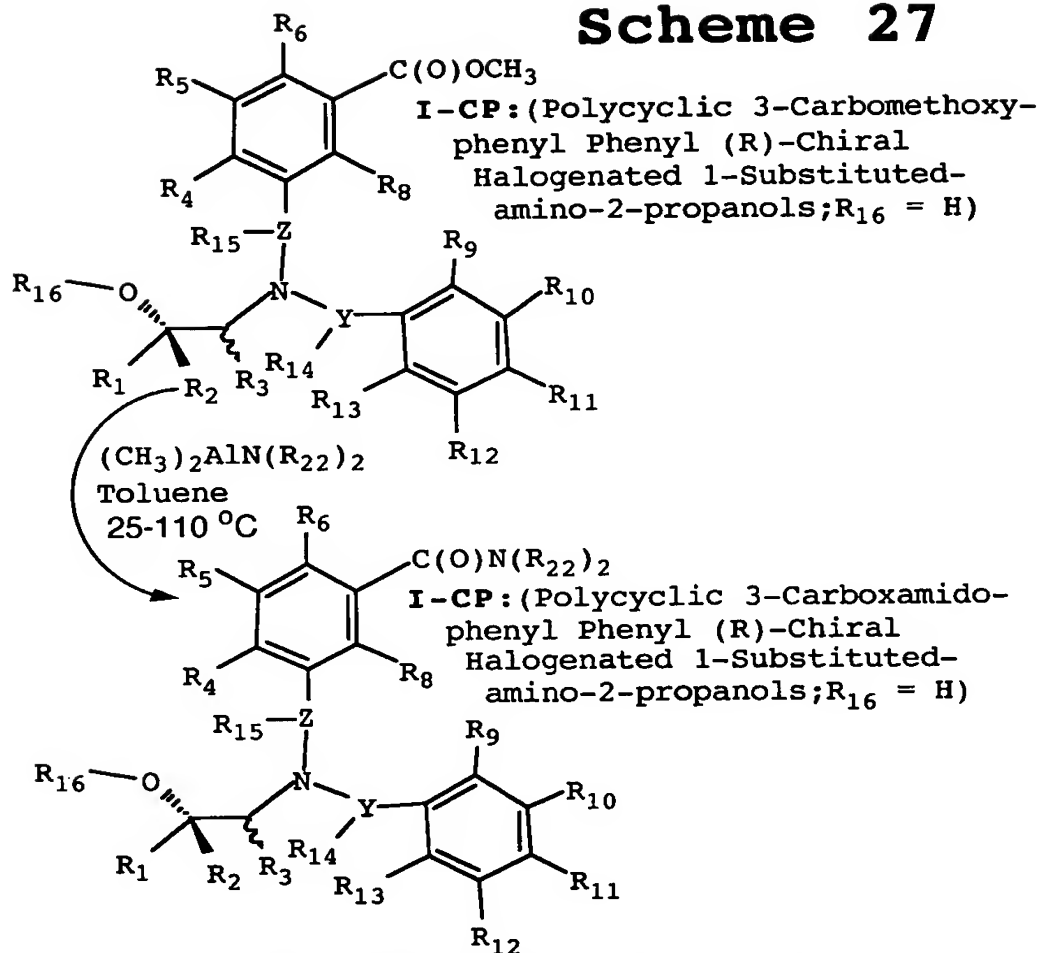
## Scheme 26

**I-CP:** (Polycyclic 3-(Unsaturated nitrogen heterocycl-1-yl)phenyl Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols;  $R_{16} = H$ )



**I-CP:** (Polycyclic 3-Aminophenyl Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols;  $R_{16} = H$ )

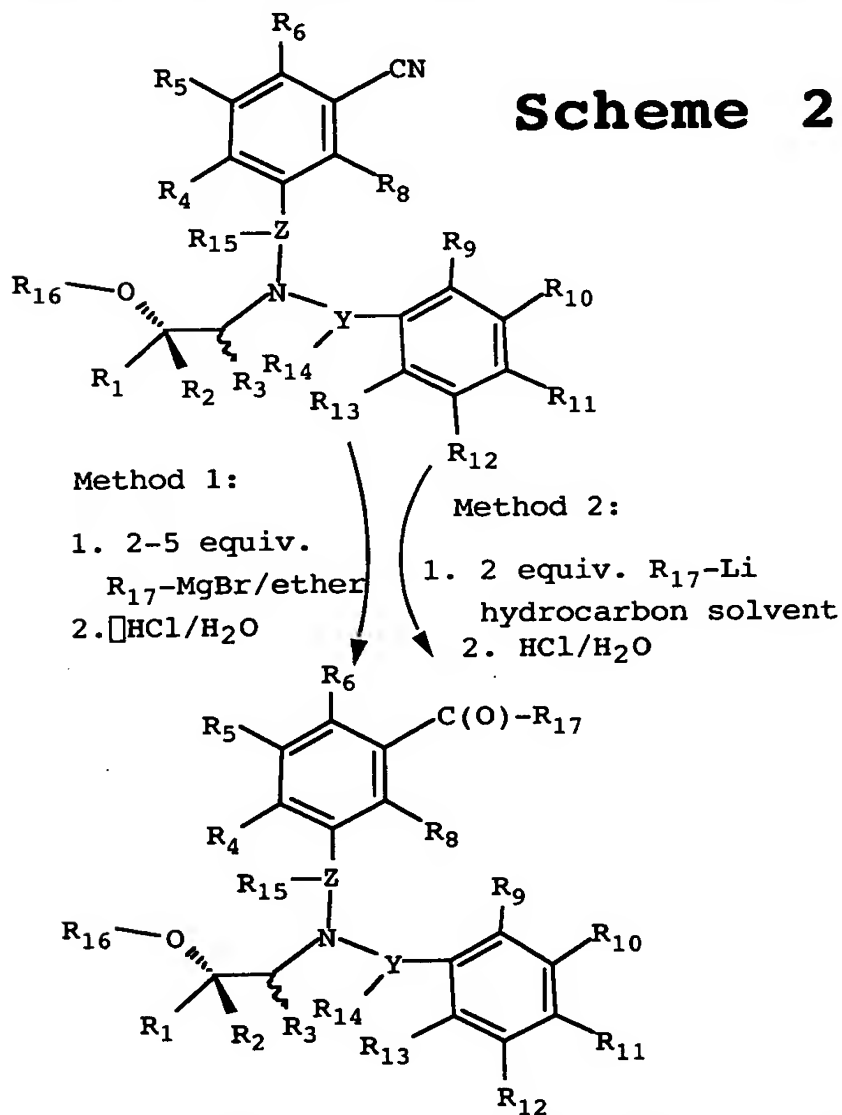
## Scheme 27



$R_{22}$  is selected independently from any one or two of the following groups: hydrido, hydroxy, aryloxy, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, alkoxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkoxy, halocycloalkoxyalkyl, heteroaryl, arylsulfinylalkyl, arylsulfonylalkyl, alkylamino, cycloalkylsulfinylalkyl, cycloalkylsulfonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, hydroxyalkyl, amino, alkoxy, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkenyl, halocycloalkenyloxyalkyl, heteroarylalkyl, and heteroarylthioalkyl.

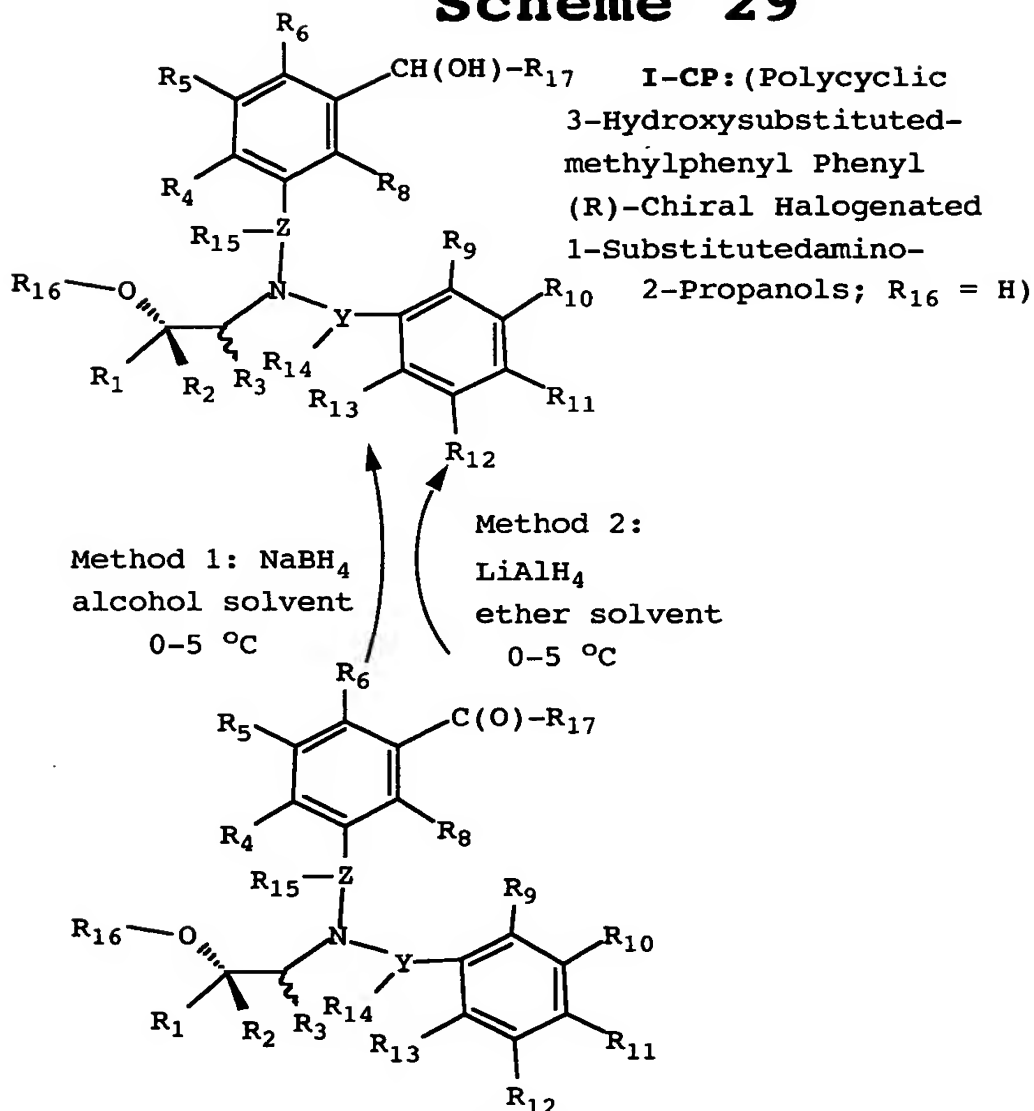
**I-CP:**(Polycyclic 3-Cyanophenyl Phenyl (R)-Chiral  
Halogenated 1-Substitutedamino-2-Propanols;  $R_{16} = H$ )

## Scheme 28



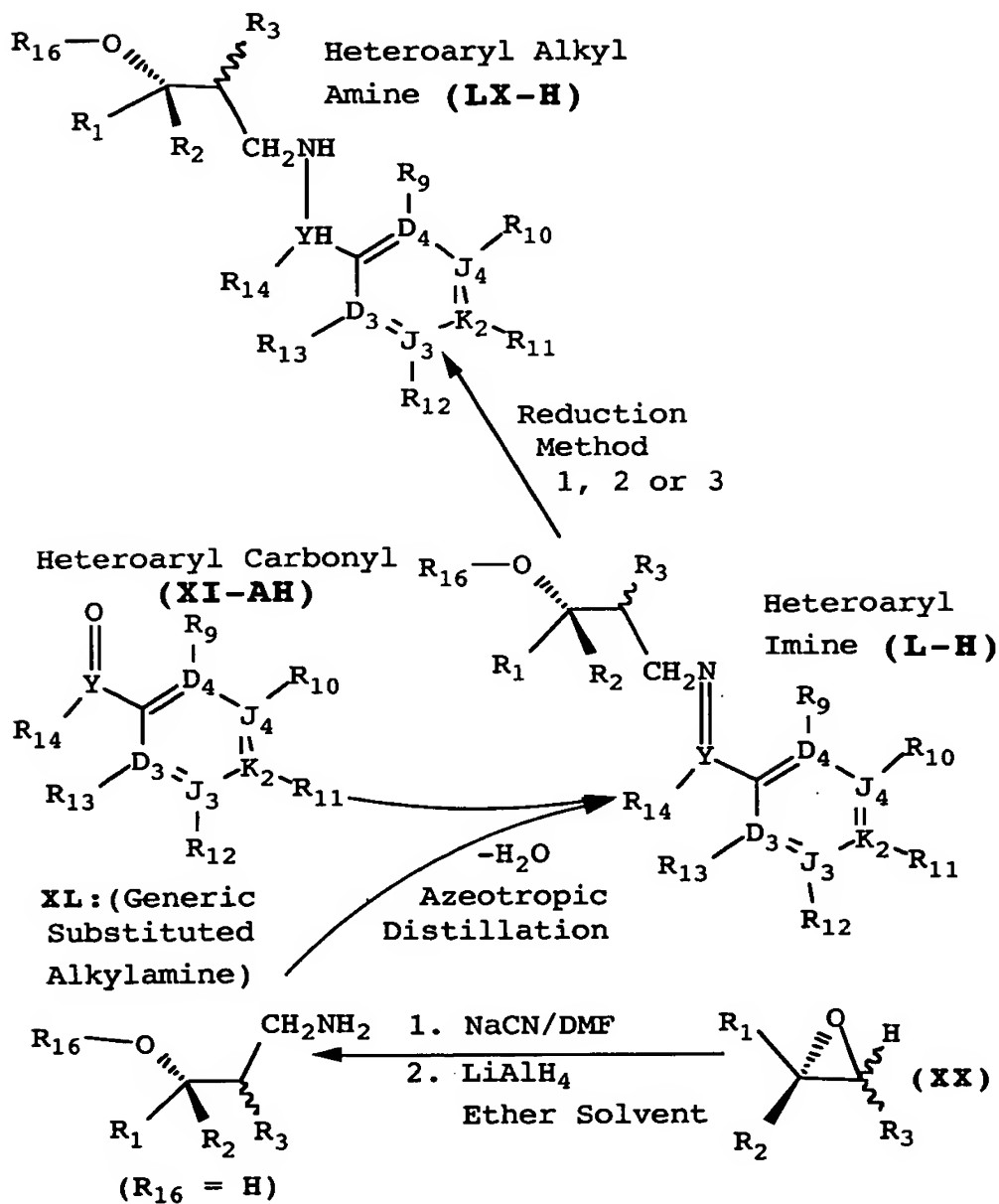
**I-CP:**(Polycyclic 3-Acylphenyl Phenyl (R)-Chiral  
Halogenated 1-Substitutedamino-2-Propanols;  $R_{16} = H$ )  
 $R_{17}$  is selected from alkyl, alkenyl, alkynyl, aryl,  
aryloxyalkyl, aralkoxyalkyl, aralkylthioalkyl,  
heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl,  
cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl,  
heteroaryl, heteroarylalkyl, heteroarylthioalkyl,  
heteroaralkylthioalkyl, heteroaralkylthioalkyl,  
alkoxyalkyl, cycloalkenylalkyl, arylthioalkyl,  
aralkyl, and cycloalkenyl.

## Scheme 29



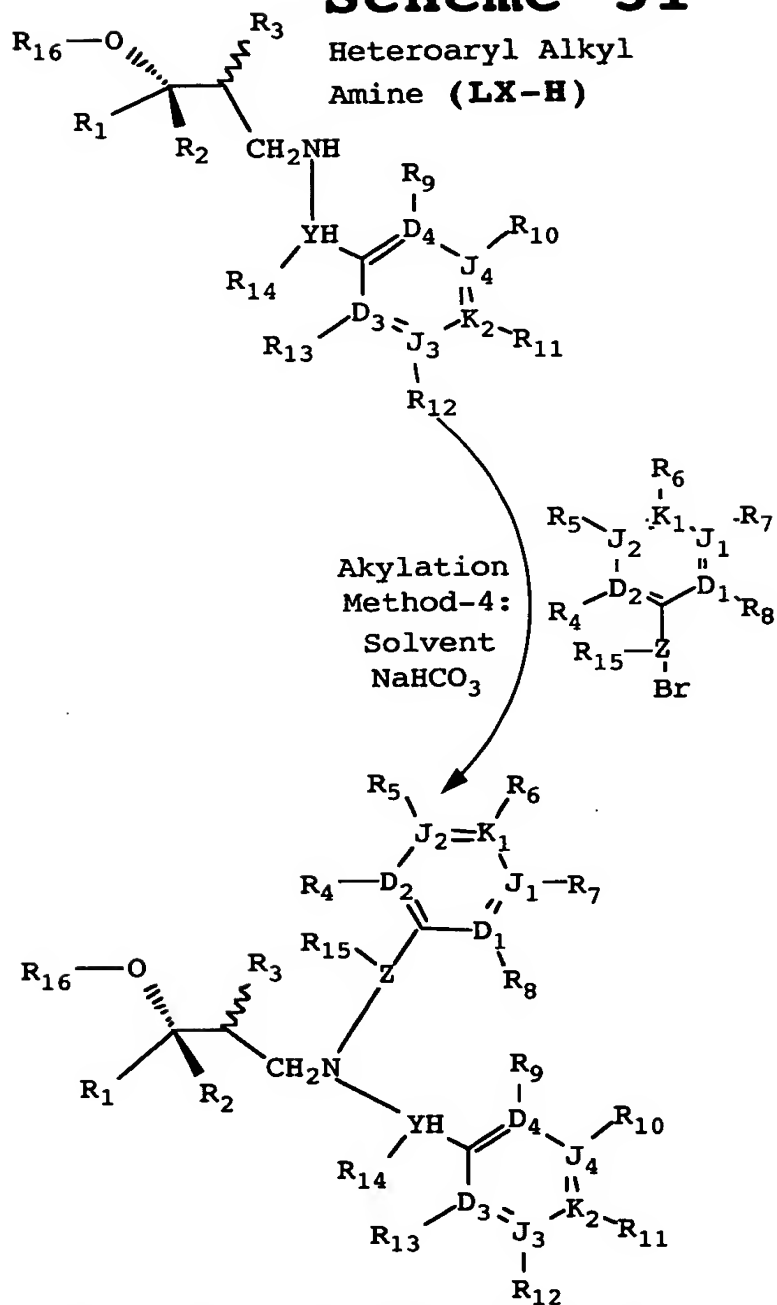
$R_{17}$  is selected from alkyl, alkenyl, alkynyl, aryl, aryloxyalkyl, aralkoxyalkyl, aralkylthioalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, aralkyl, heteroaralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl, cycloalkenylalkyl, arylthioalkyl, and cycloalkenyl.

## Scheme 30



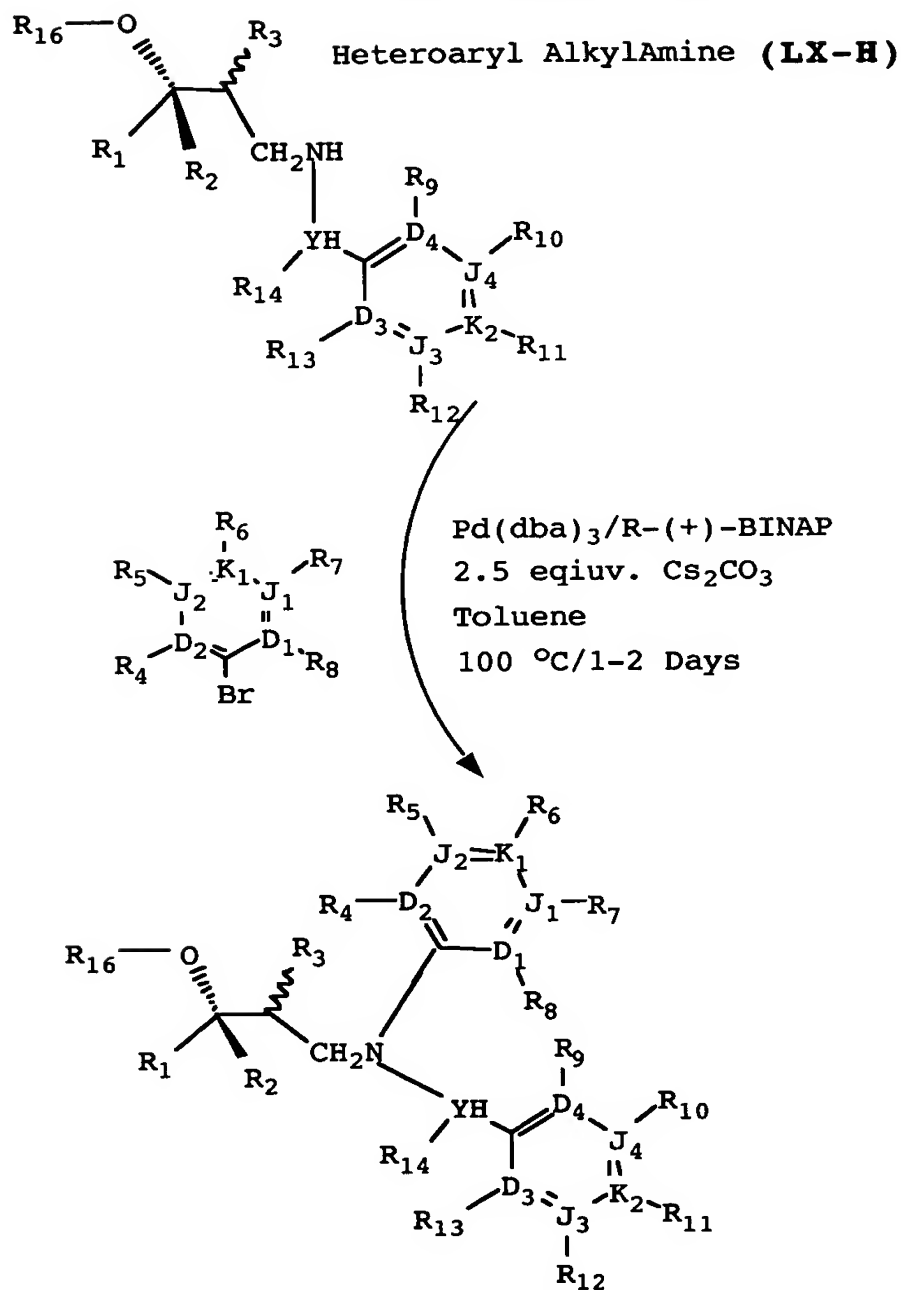


# Scheme 31



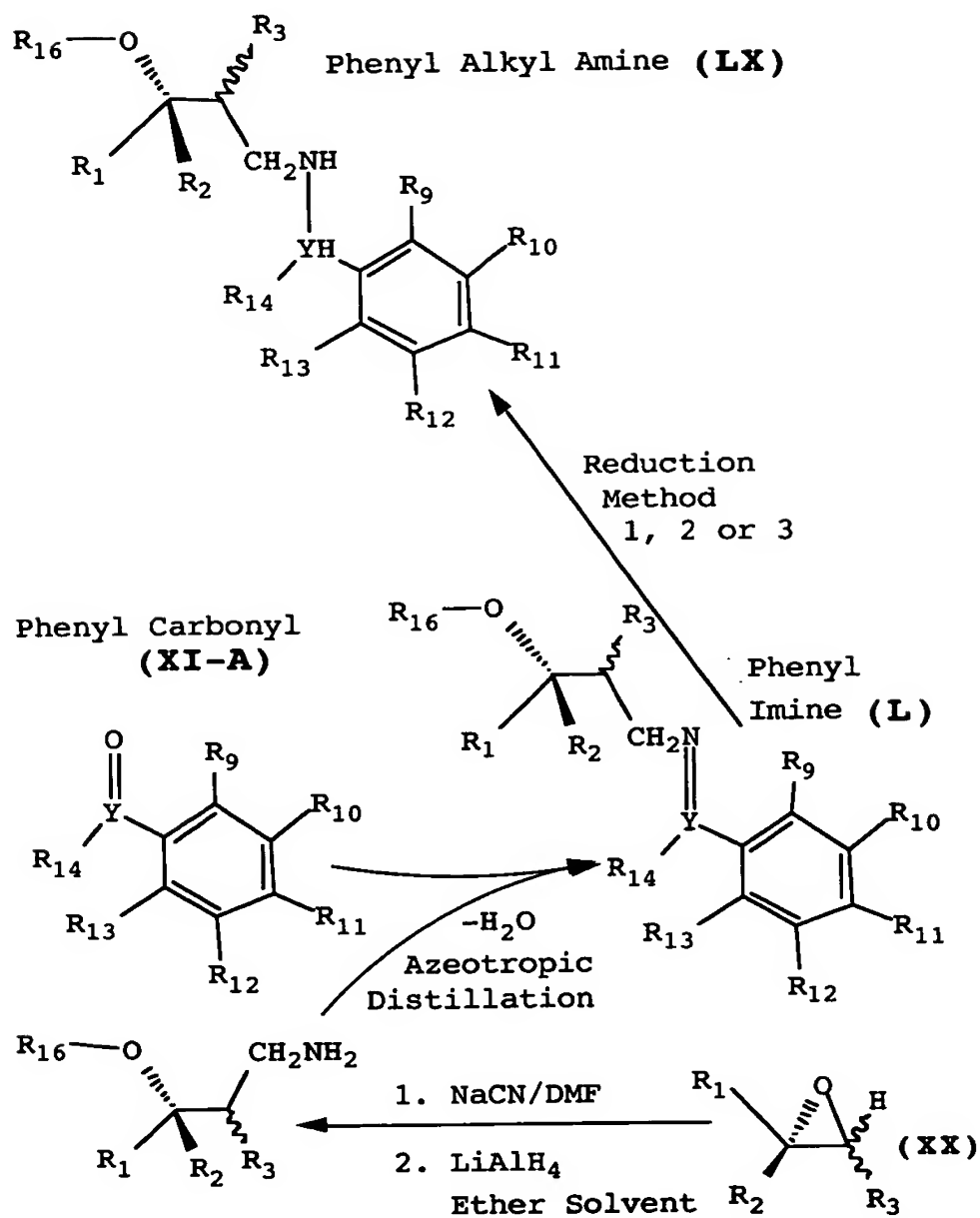
# Scheme 32

Heteroaryl AlkylAmine (LX-H)



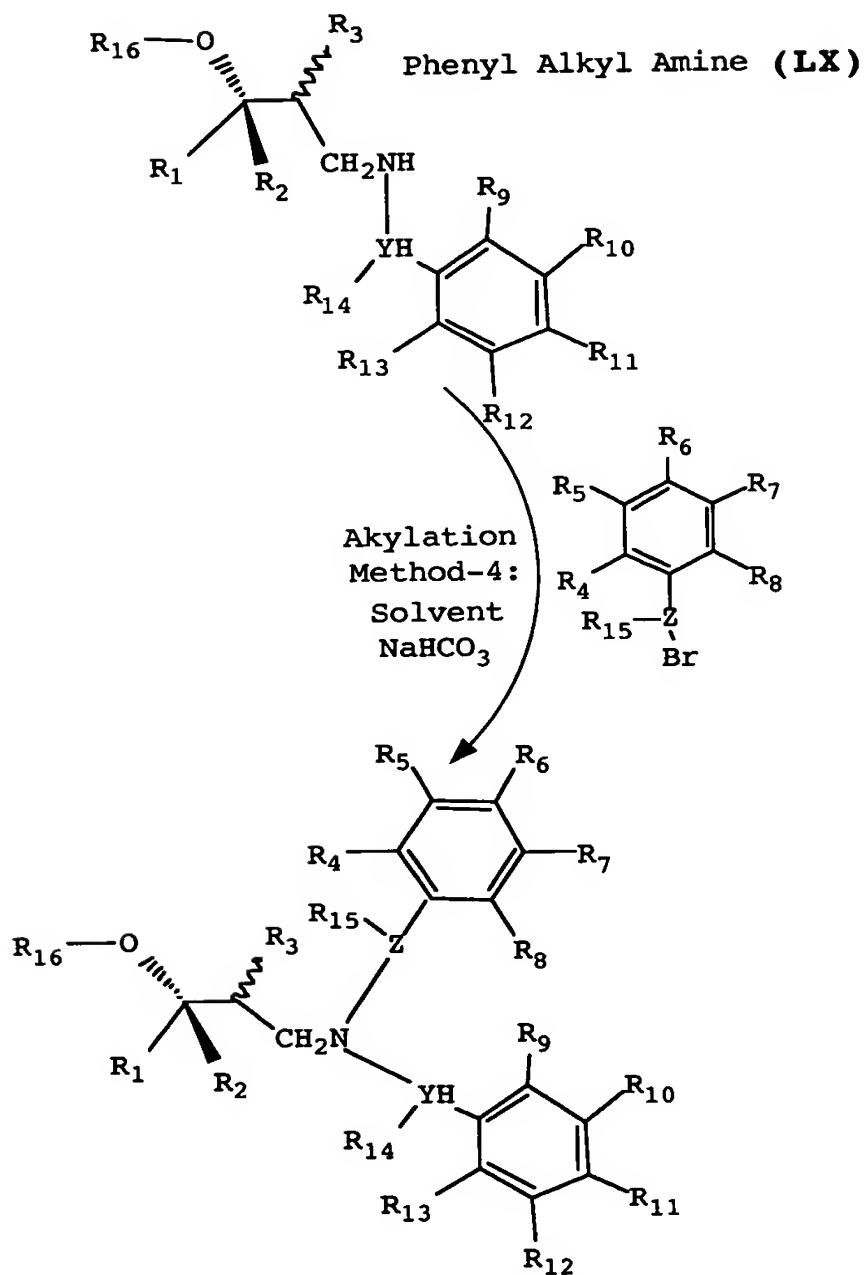
I-H: (Generic Polycyclic Aryl and Heteroaryl (R)-Chiral Halogenated 1-Substitutedamino-3-Butanols)

# Scheme 33



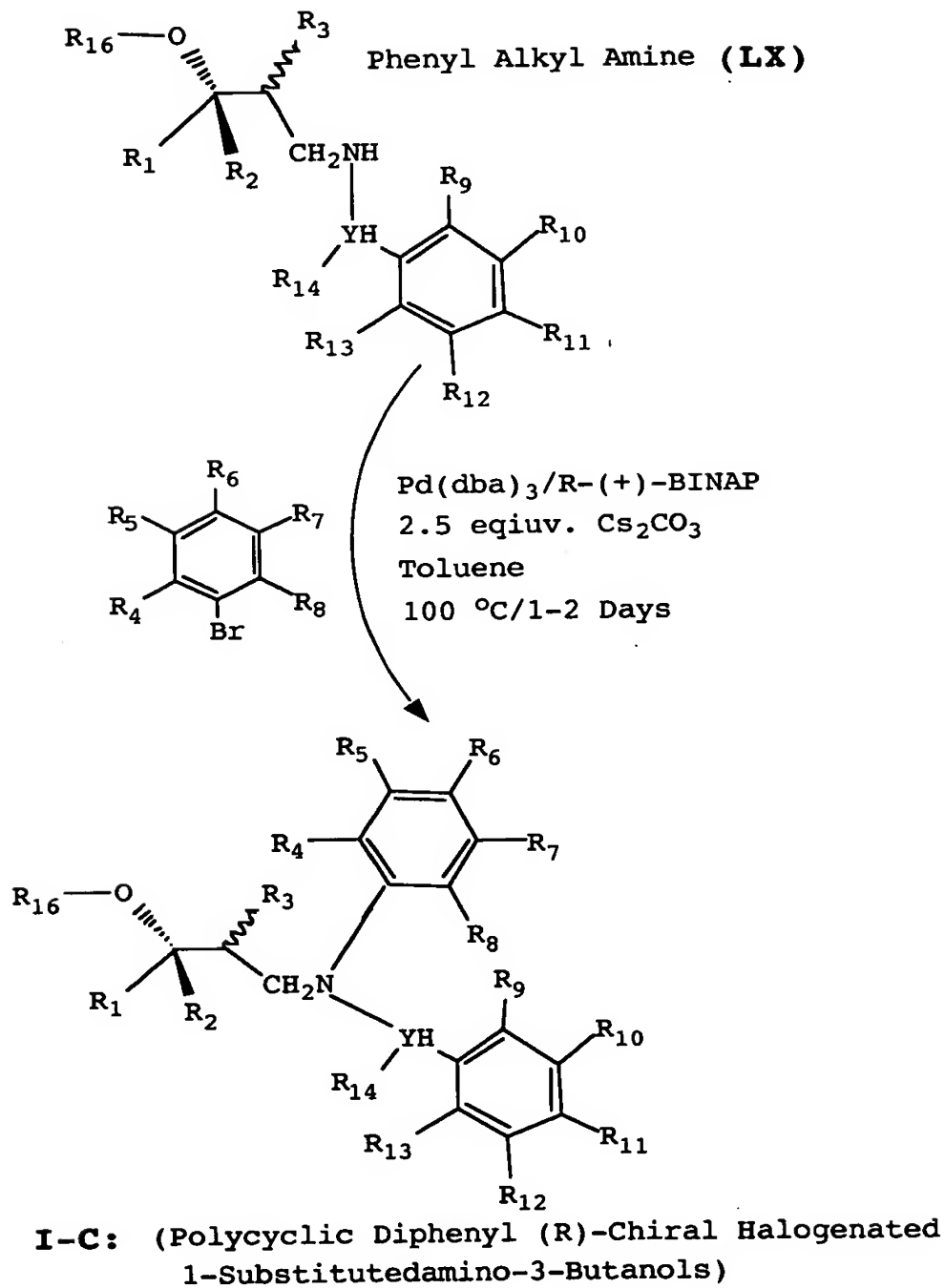
XL: (Generic Substituted Alkylamine; R<sub>16</sub> = H)

# Scheme 34



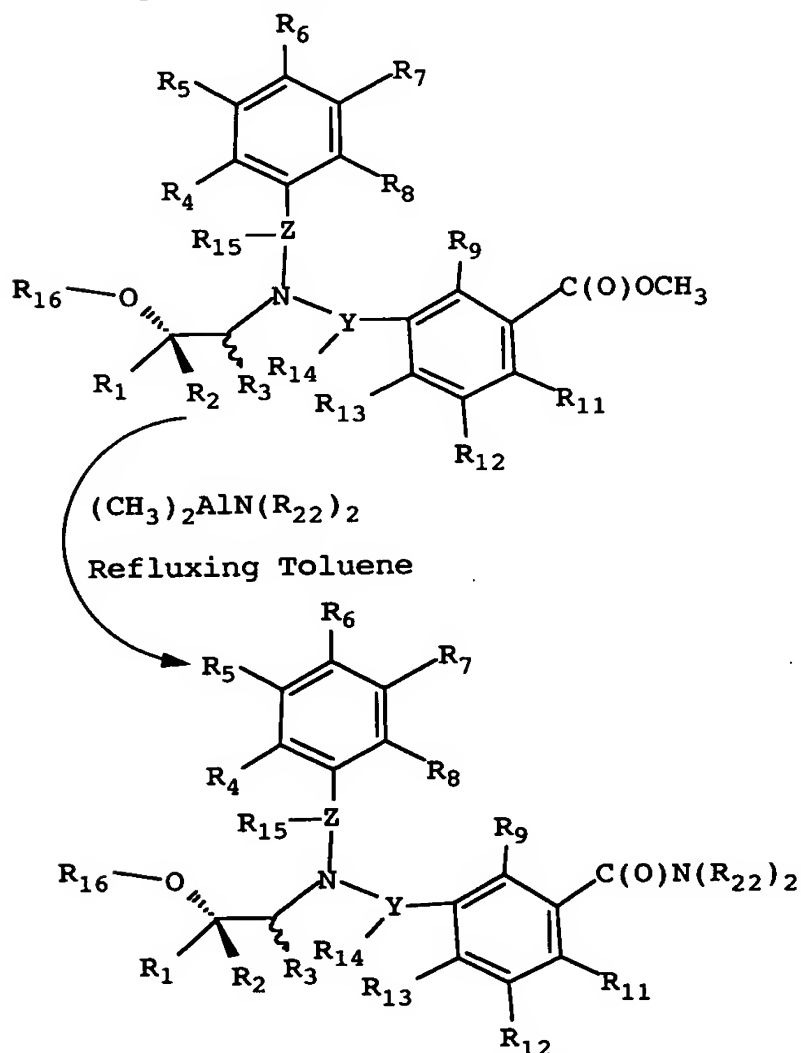
**I-C: (Polycyclic Diphenyl (R)-Chiral Halogenated 1-Substitutedamino-3-Butanols)**

# Scheme 35



## Scheme 36

**I-CP:** (Polycyclic 3-Carbomethoxyaryl Phenyl  
(R)-Chiral Halogenated 1-Substitutedamino-  
2-Propanols;  $R_{16} = H$ )

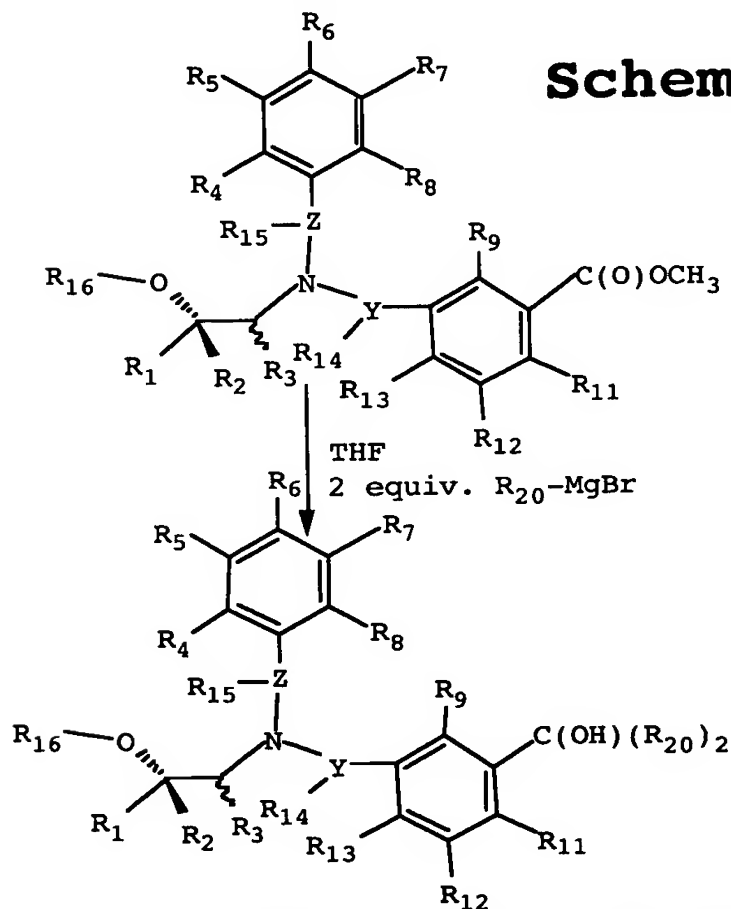


**I-CP:** (Polycyclic 3-Carboxamidoaryl Phenyl  
(R)-Chiral Halogenated 1-Substitutedamino-  
2-Propanols;  $R_{16} = H$ )

NOTE:  $R_{22}$  is as defined in Scheme 27

**I-CP:** (Polycyclic 3-Carbomethoxyaryl Phenyl  
(R)-Chiral Halogenated 1-Substitutedamino-  
2-Propanols;  $R_{16} = H$ )

## Scheme 37

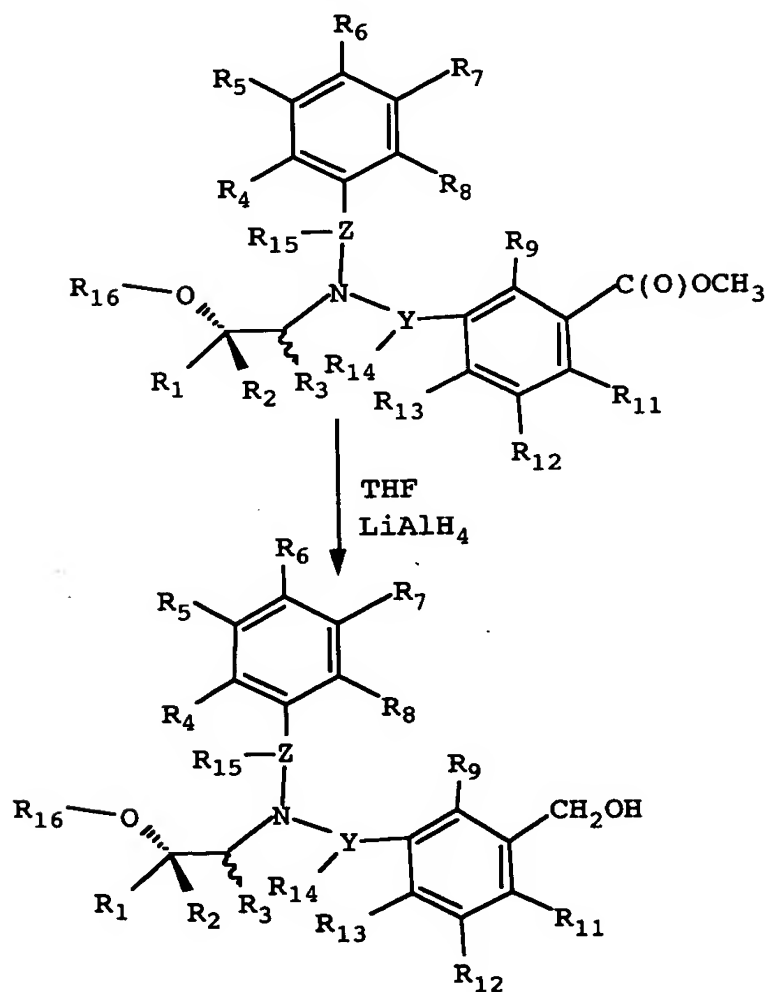


**I-CP:** (Polycyclic 3-(bis- $R_{20}$ -hydroxymethyl)aryl  
Phenyl (R)-Chiral Halogenated 1-Substitutedamino-  
2-Propanols;  $R_{16} = H$ )

$R_{20}$  is selected from alkyl, alkenyl, alkynyl, aryl, aryloxyalkyl, aralkoxyalkyl, aralkylthioalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, heteroaralkylthioalkyl, cycloalkenylalkyl, arylthioalkyl, aralkyl, alkoxyalkyl, and cycloalkenyl.

## Scheme 38

**I-CP:** (Polycyclic 3-Carbomethoxyaryl Phenyl  
(R)-Chiral Halogenated 1-Substitutedamino-  
2-Propanols;  $R_{16} = H$ )

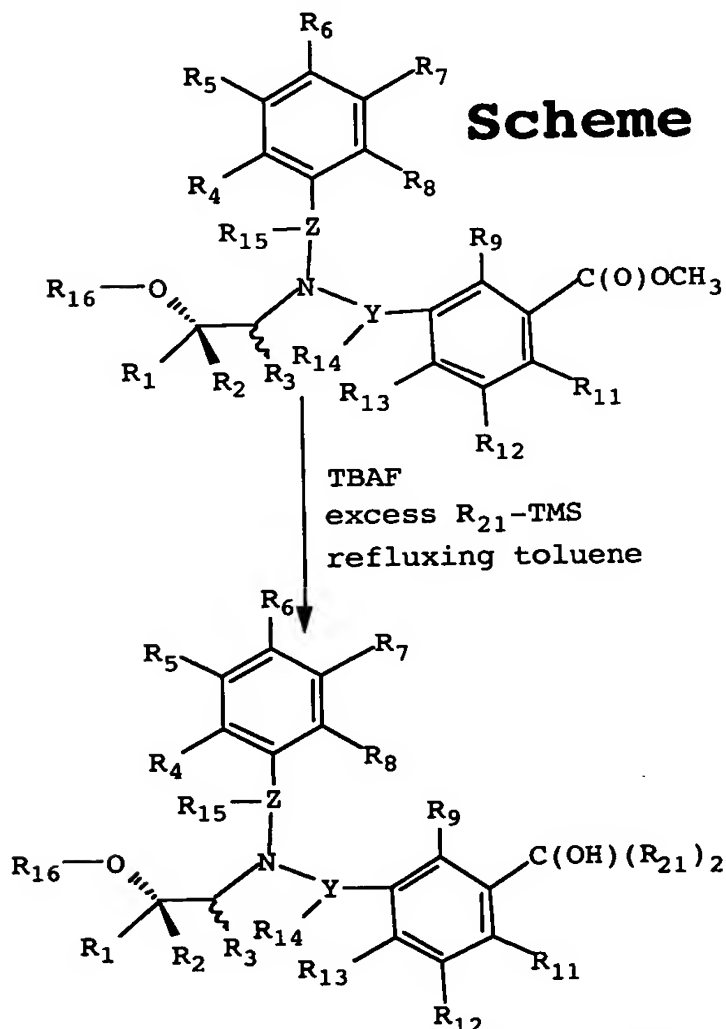


**I-CP:** (Polycyclic 3-Hydroxymethylaryl Phenyl  
(R)-Chiral Halogenated 1-Substitutedamino-  
2-Propanols;  $R_{16} = H$ )



**I-CP:** (Polycyclic 3-Carbomethoxyaryl Phenyl  
(R)-Chiral Halogenated 1-Substitutedamino-  
2-Propanols;  $R_{16} = H$ )

### Scheme 39



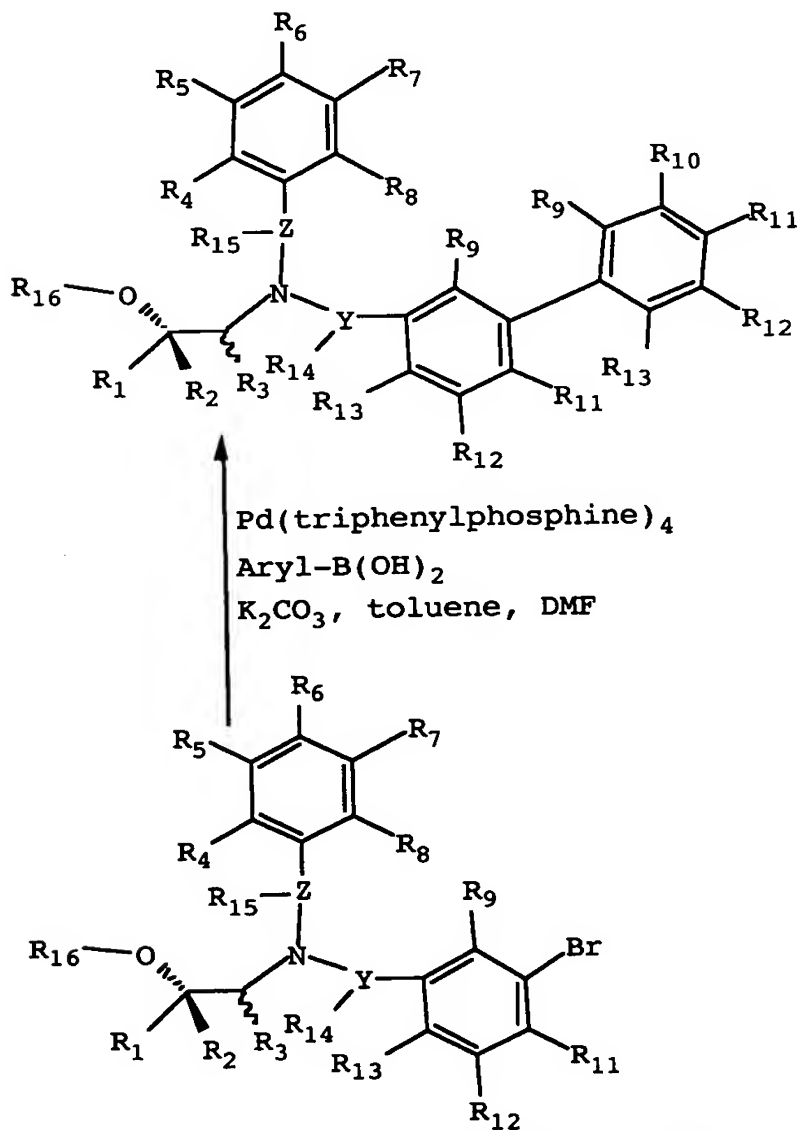
**I-CP:** (Polycyclic 3-(bis- $R_{21}$ -hydroxymethyl)aryl  
Phenyl (R)-Chiral Halogenated 1-Substitutedamino-  
2-Propanols;  $R_{16} = H$ )

$R_{21}$  is selected from perfluoroalkyl, perfluoroalkenyl,  
perfluorocycloalkyl, perfluorocycloalkylalkyl,  
perfluoroaralkyl, perfluoroalkoxyalkyl.

*Ref*  
9-5-07

## Scheme 40

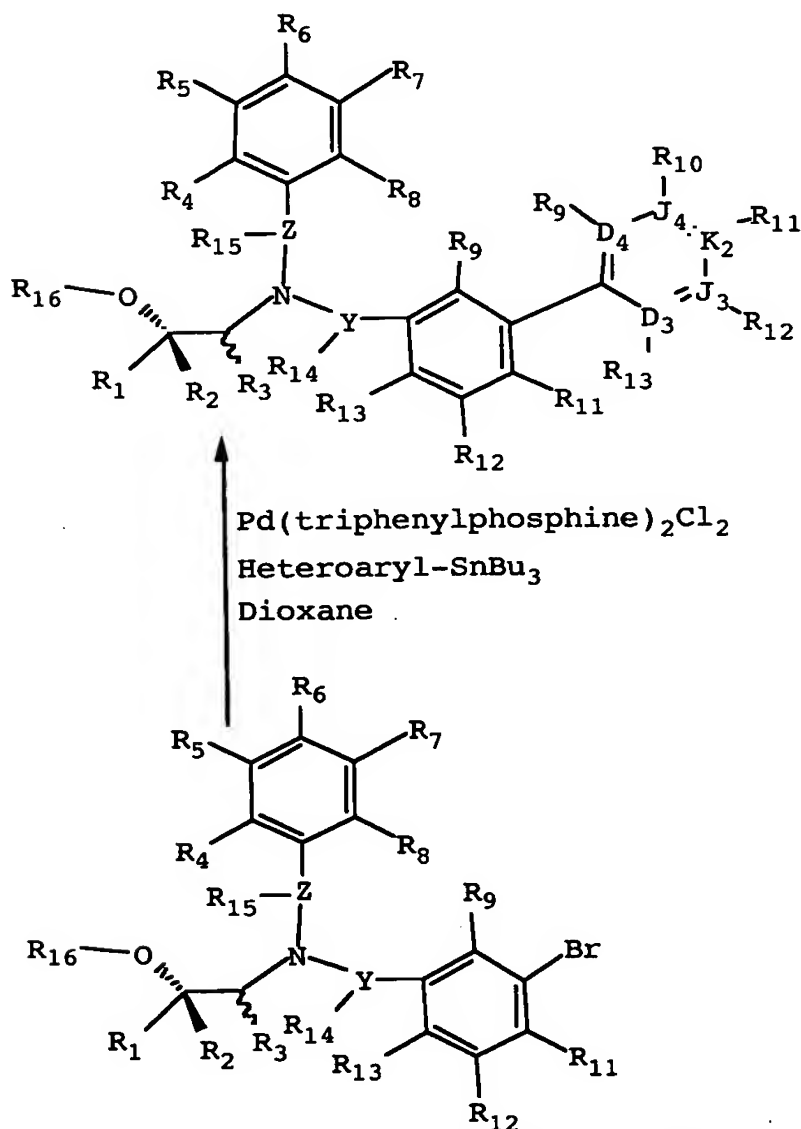
**I-CP:** (Polycyclic 3-Arylaryl Phenyl  
(R)-Chiral Halogenated 1-Substitutedamino-  
2-Propanols;  $R_{16} = H$ )



**I-CP:** (Polycyclic 3-Bromoaryl Phenyl  
(R)-Chiral Halogenated 1-Substitutedamino-  
2-Propanols;  $R_{16} = H$ )

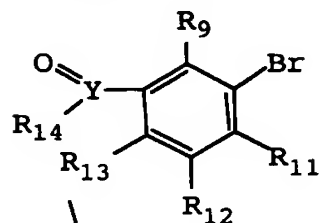
## Scheme 41

**I-CP:** (Polycyclic 3-Heteroarylaryl Phenyl  
(R)-Chiral Halogenated 1-Substitutedamino-  
2-Propanols;  $R_{16} = H$ )

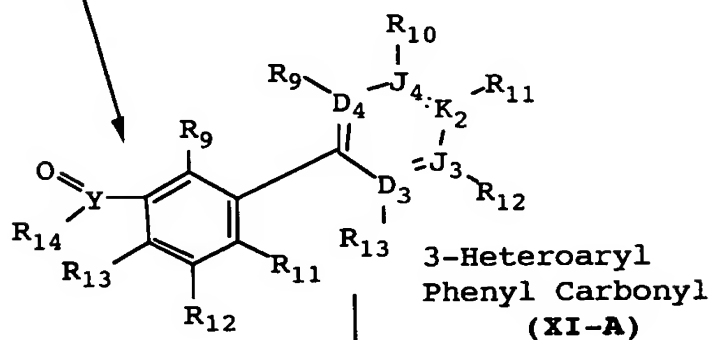


**I-CP:** (Polycyclic 3-Bromoaryl Phenyl  
(R)-Chiral Halogenated 1-Substitutedamino-  
2-Propanols;  $R_{16} = H$ )

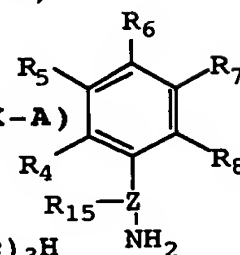
## Scheme 42

3-Bromo Phenyl  
Carbonyl (XI-A)

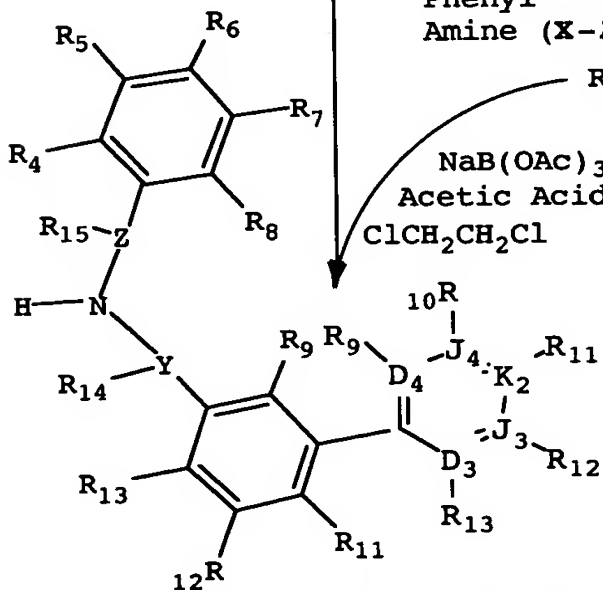
$\text{Pd}(\text{triphenylphosphine})_2\text{Cl}_2$   
Heteroaryl-SnBu<sub>3</sub>, Dioxane



Phenyl  
Amine (X-A)



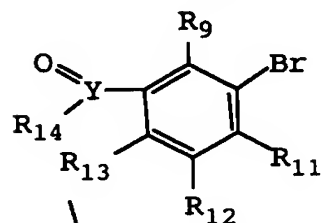
$\text{NaB}(\text{OAc})_3\text{H}$   
Acetic Acid  
 $\text{ClCH}_2\text{CH}_2\text{Cl}$



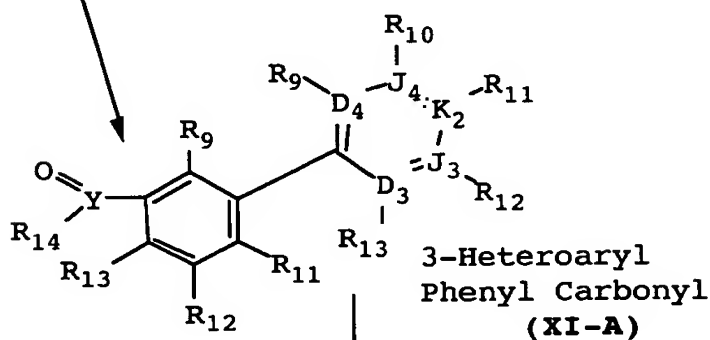
Secondary Phenyl Amine (XIII-A)

## Scheme 43

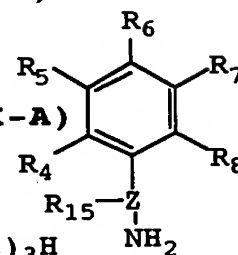
3-Bromo Phenyl  
Carbonyl (XI-A)



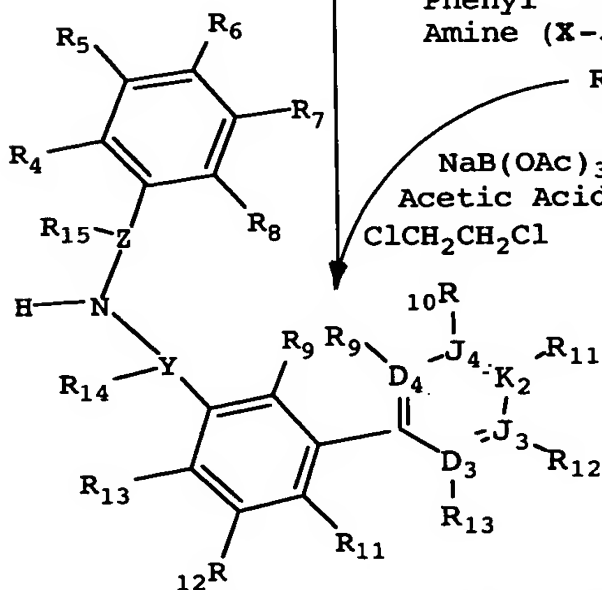
$\text{Pd}(\text{triphenylphosphine})_4$   
Heteroaryl-Br, THF,  $\text{ZnCl}_2$



Phenyl  
Amine (X-A)



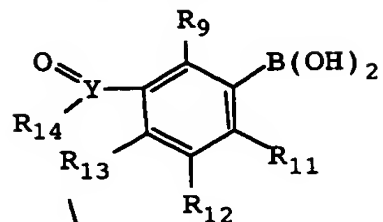
$\text{NaB}(\text{OAc})_3\text{H}$   
Acetic Acid  
 $\text{ClCH}_2\text{CH}_2\text{Cl}$



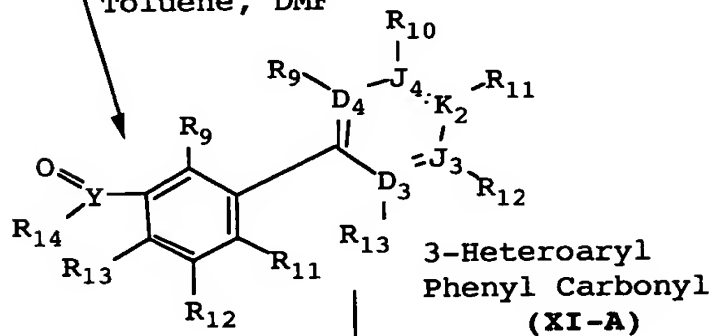
Secondary Phenyl Amine (XIII-A)

## Scheme 44

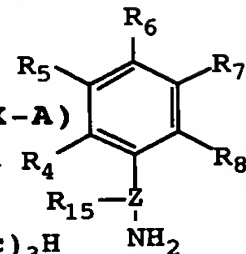
3-B(OH)<sub>2</sub> Phenyl  
Carbonyl (XI-A)



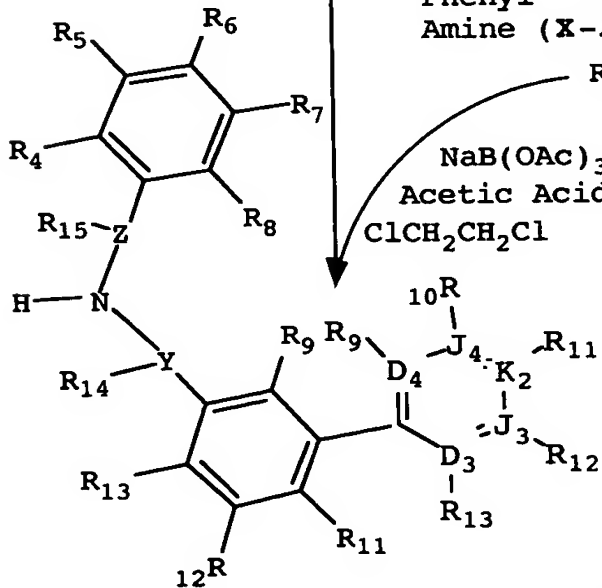
Pd(triphenylphosphine)<sub>4</sub>  
Heteroaryl-Br or Aryl-Br, K<sub>2</sub>CO<sub>3</sub>,  
Toluene, DMF



Phenyl  
Amine (X-A)

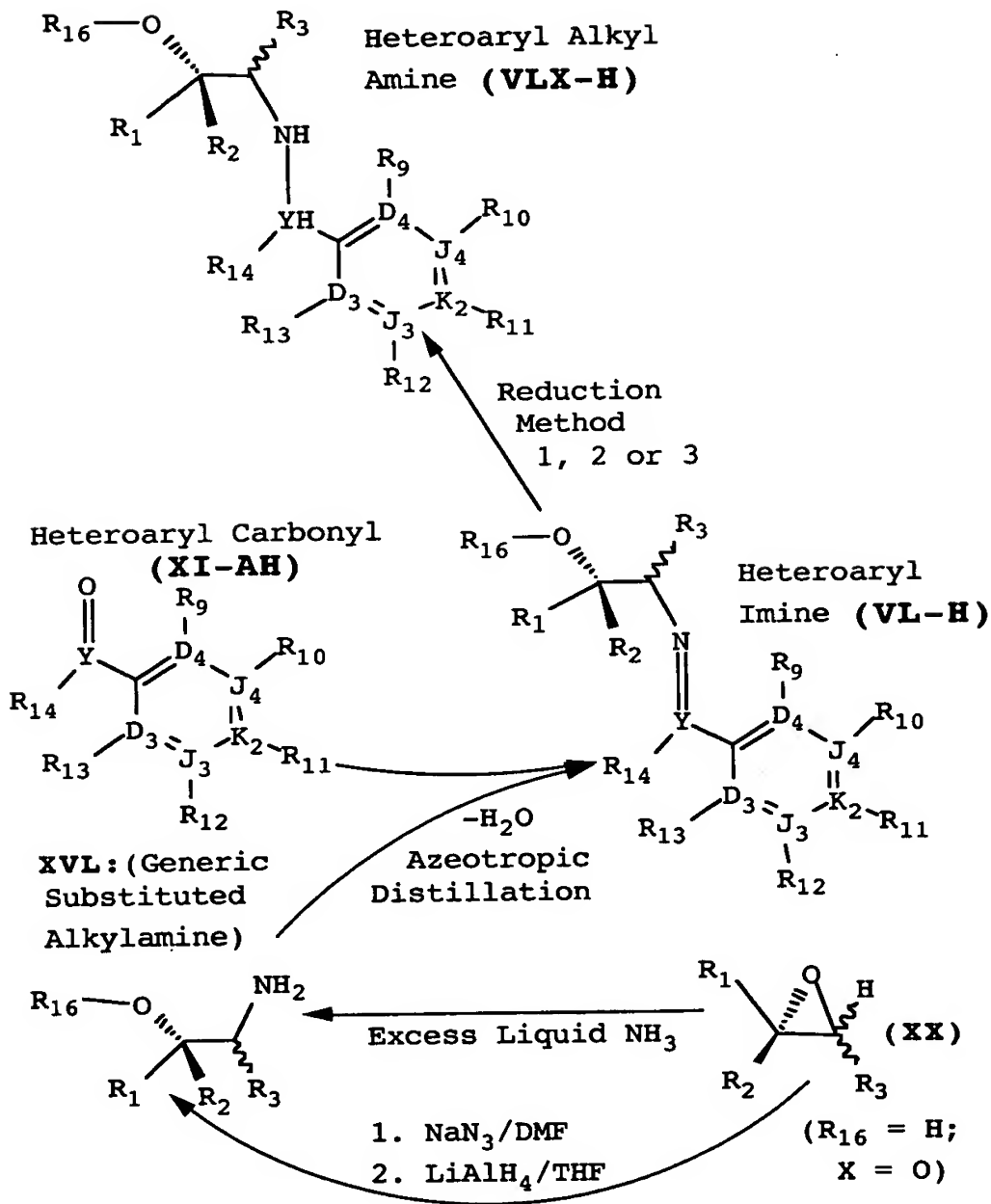


NaB(OAc)<sub>3</sub>H  
Acetic Acid  
ClCH<sub>2</sub>CH<sub>2</sub>Cl

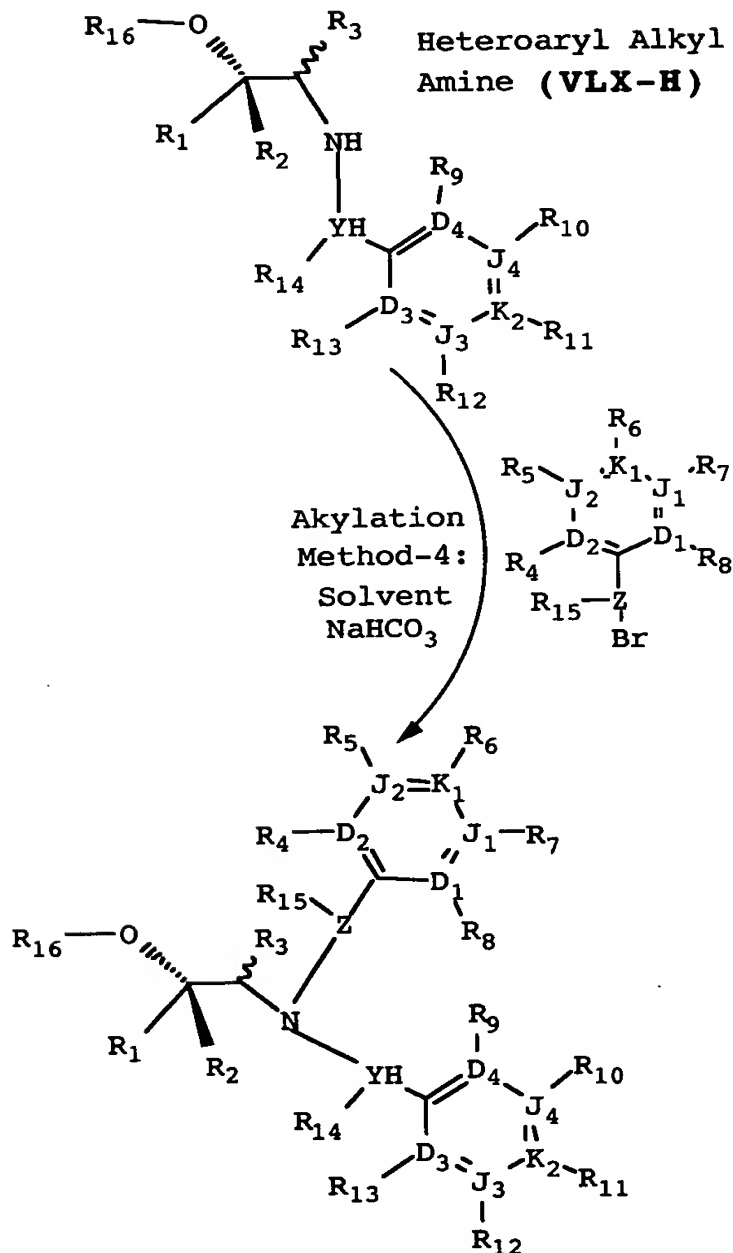


Secondary Phenyl Amine (XIII-A)

## Scheme 45



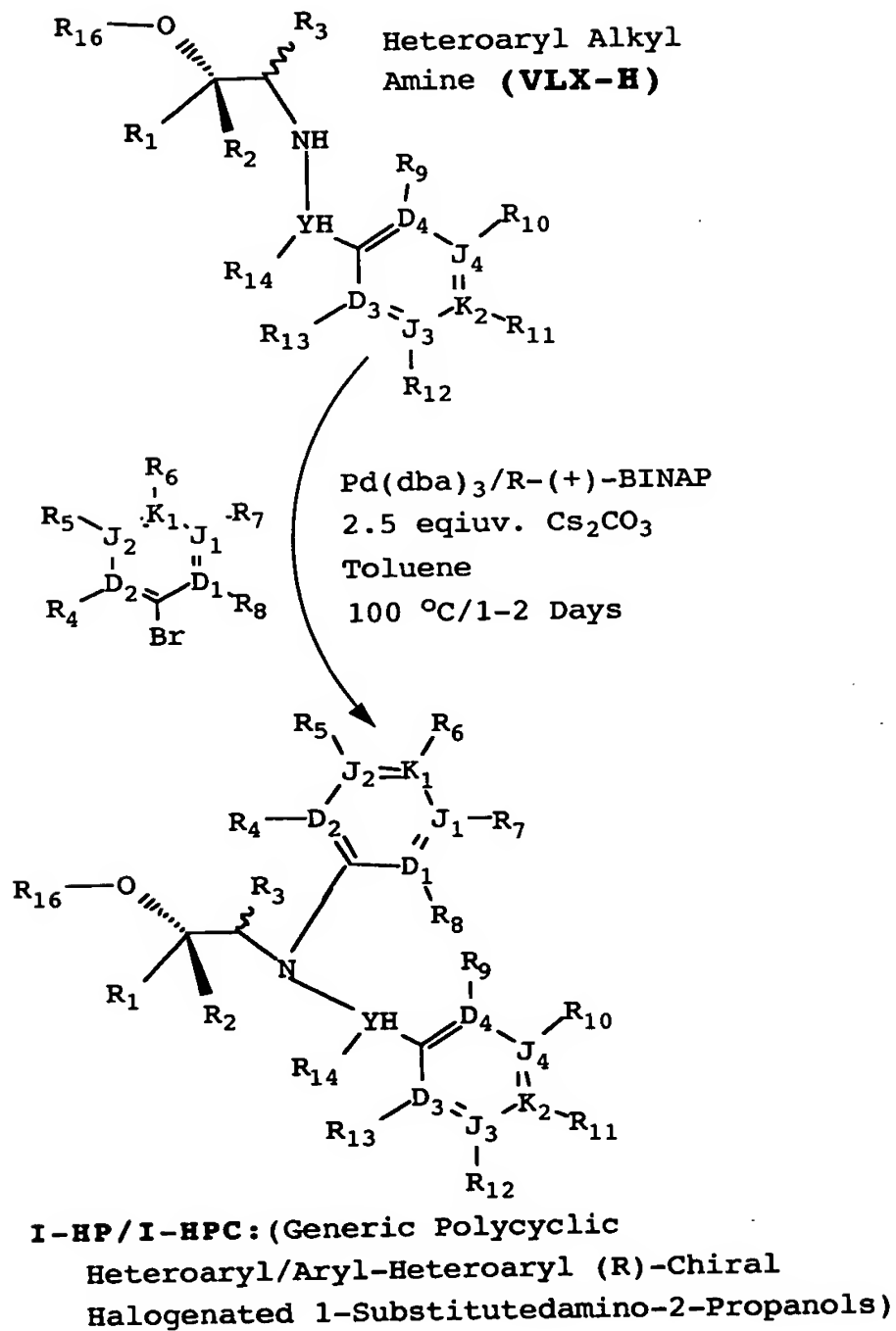
# Scheme 46



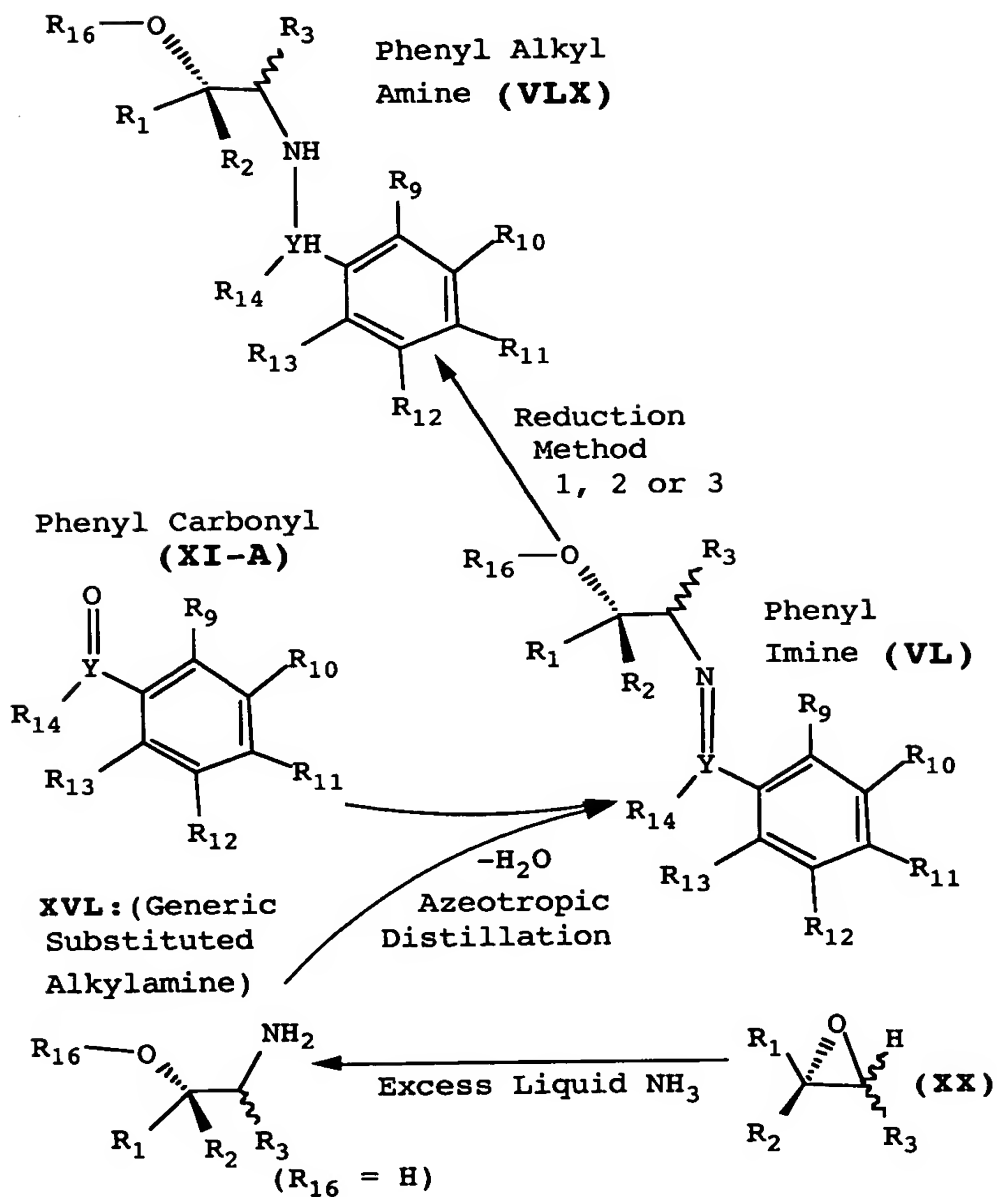
**I-HP/I-HPC:** (Generic Polycyclic  
Heteroaryl/Aryl-Heteroaryl (R)-Chiral  
Halogenated 1-Substitutedamino-2-Propanols)



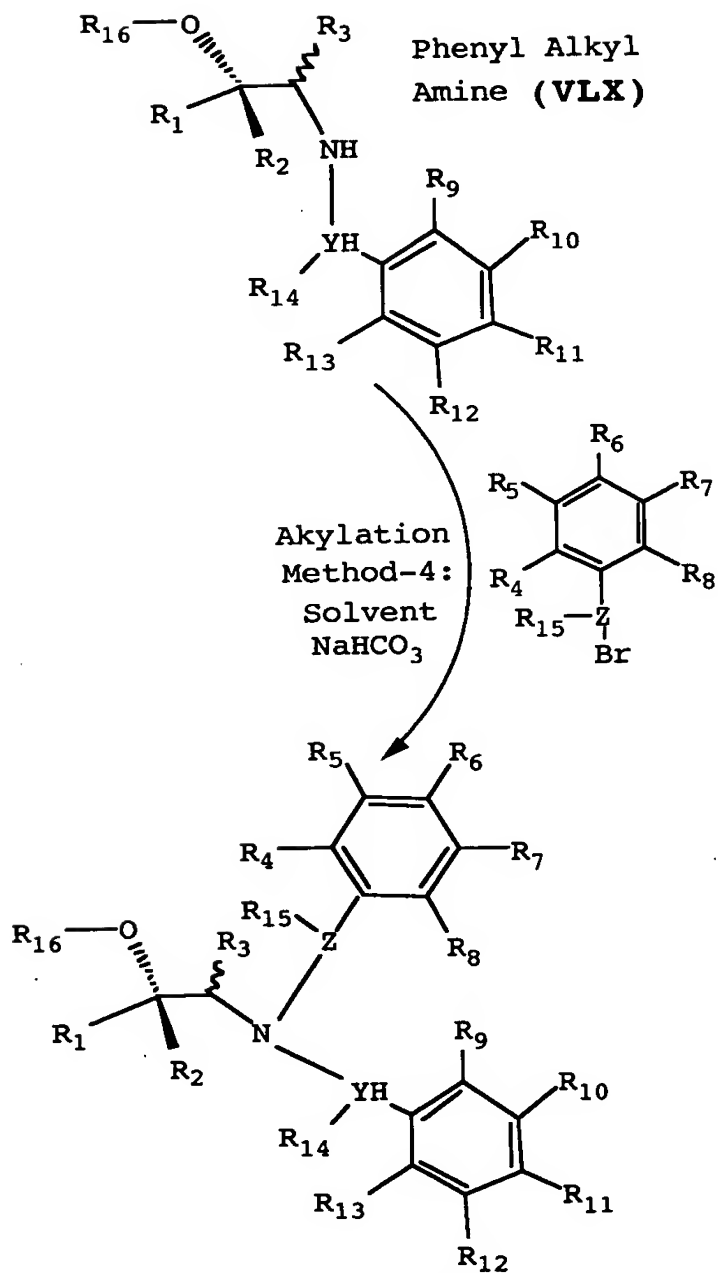
## Scheme 47



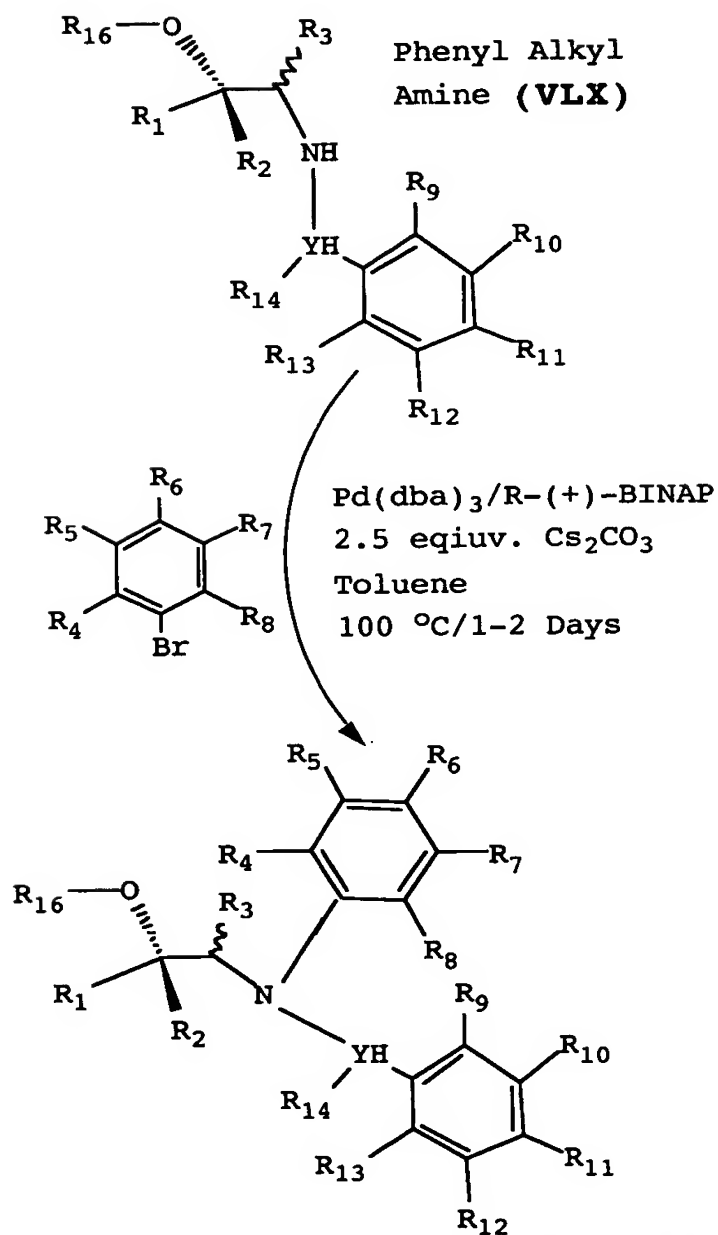
## Scheme 48



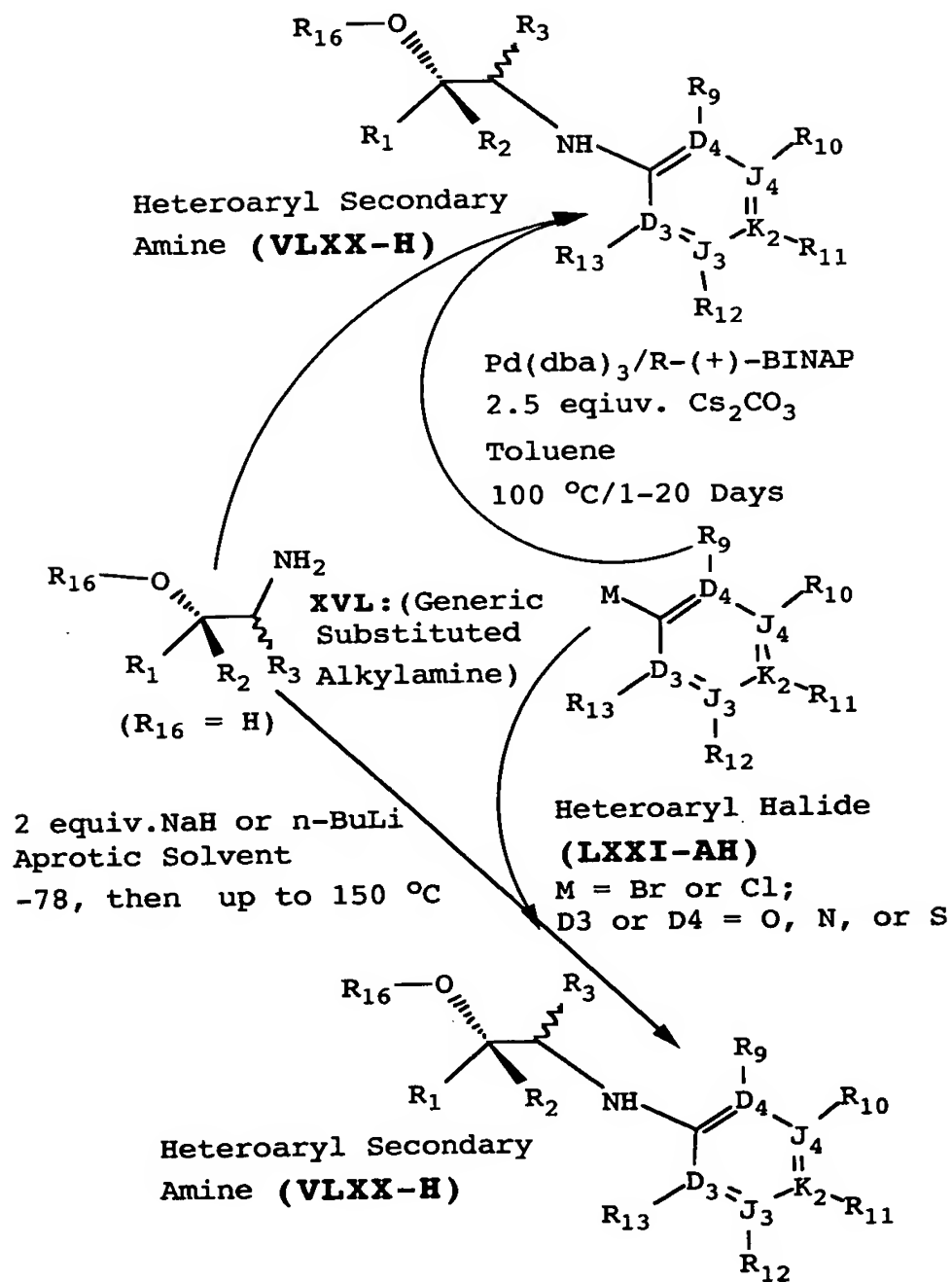
## Scheme 49



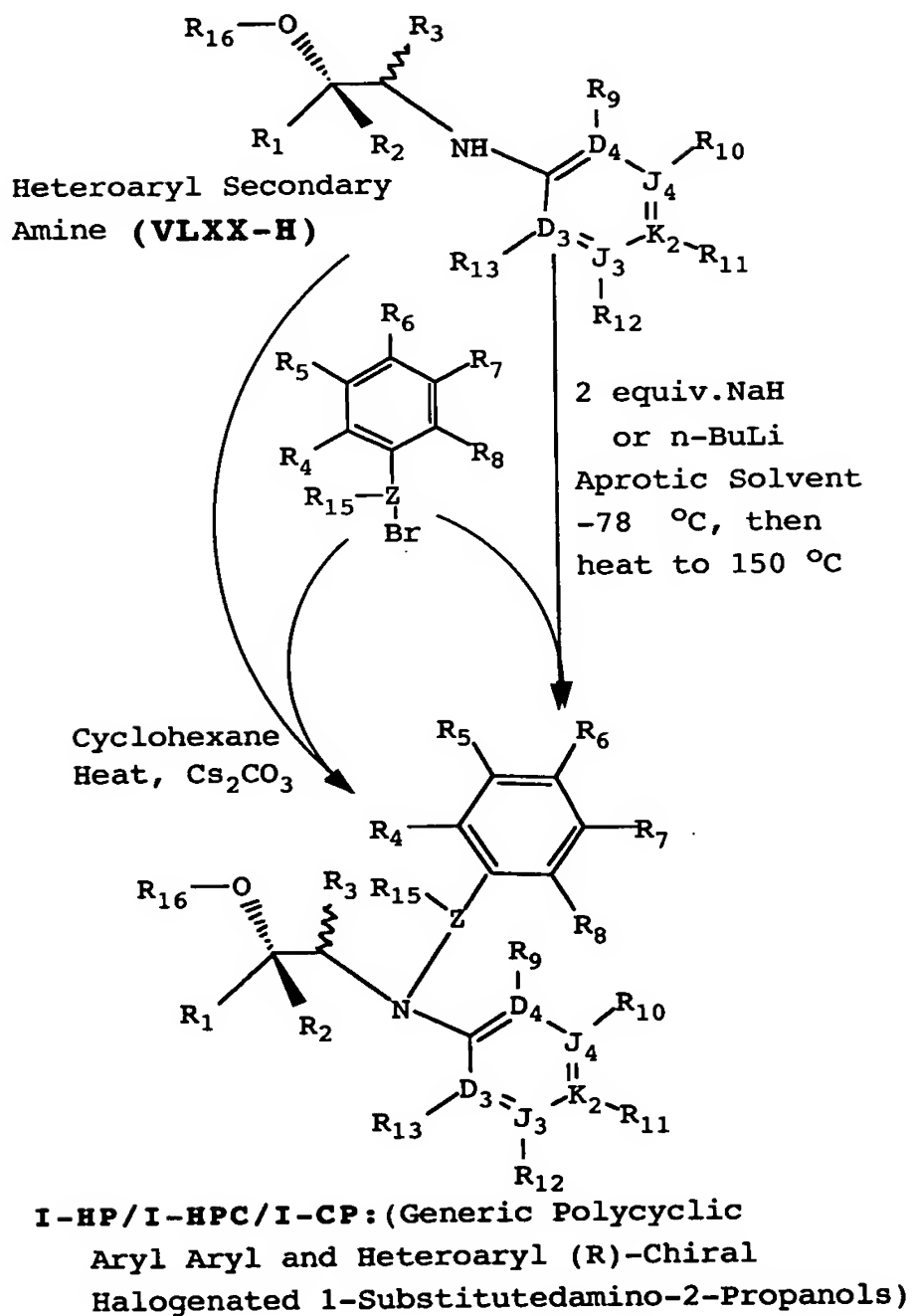
# Scheme 50



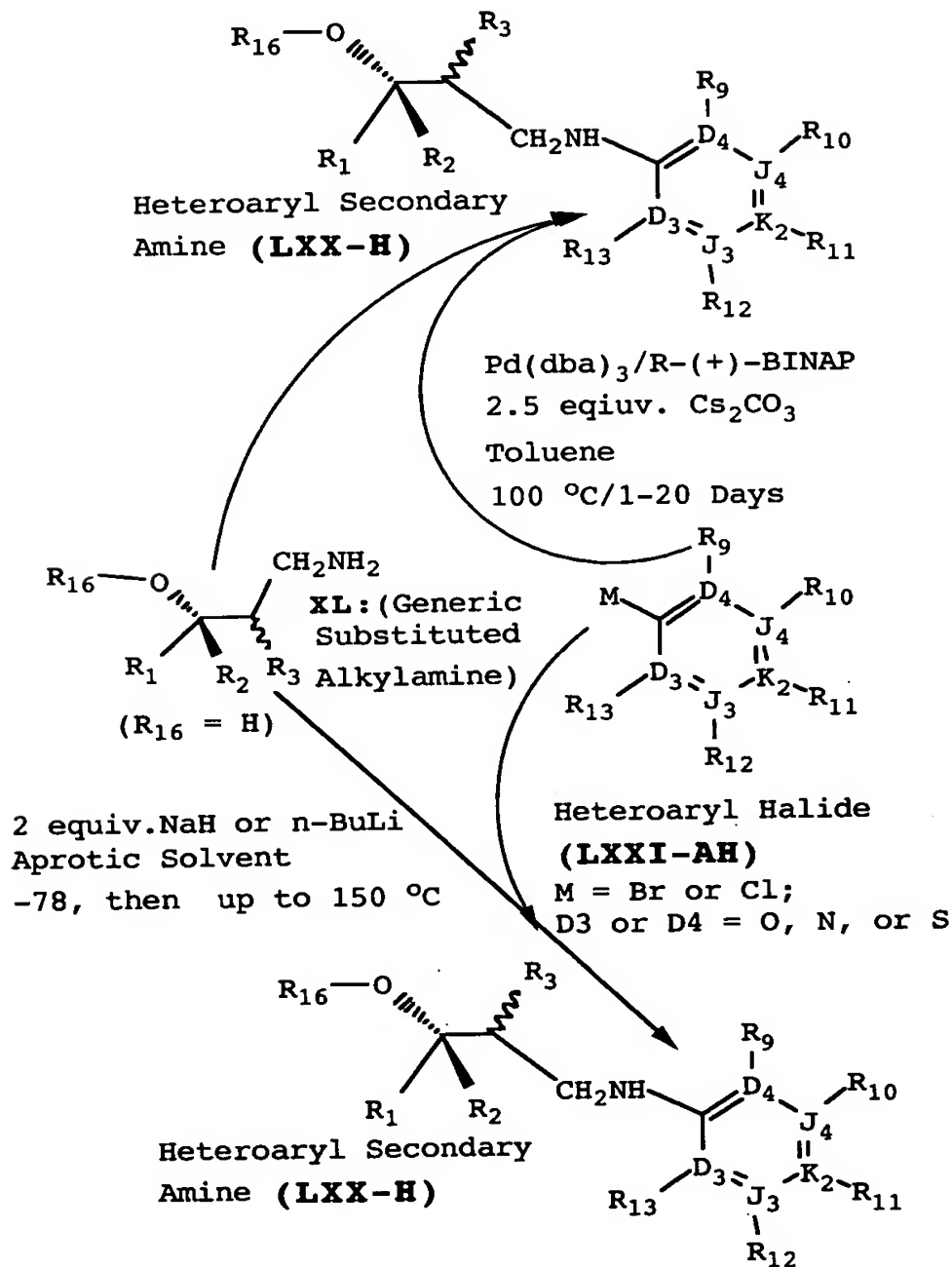
## Scheme 51



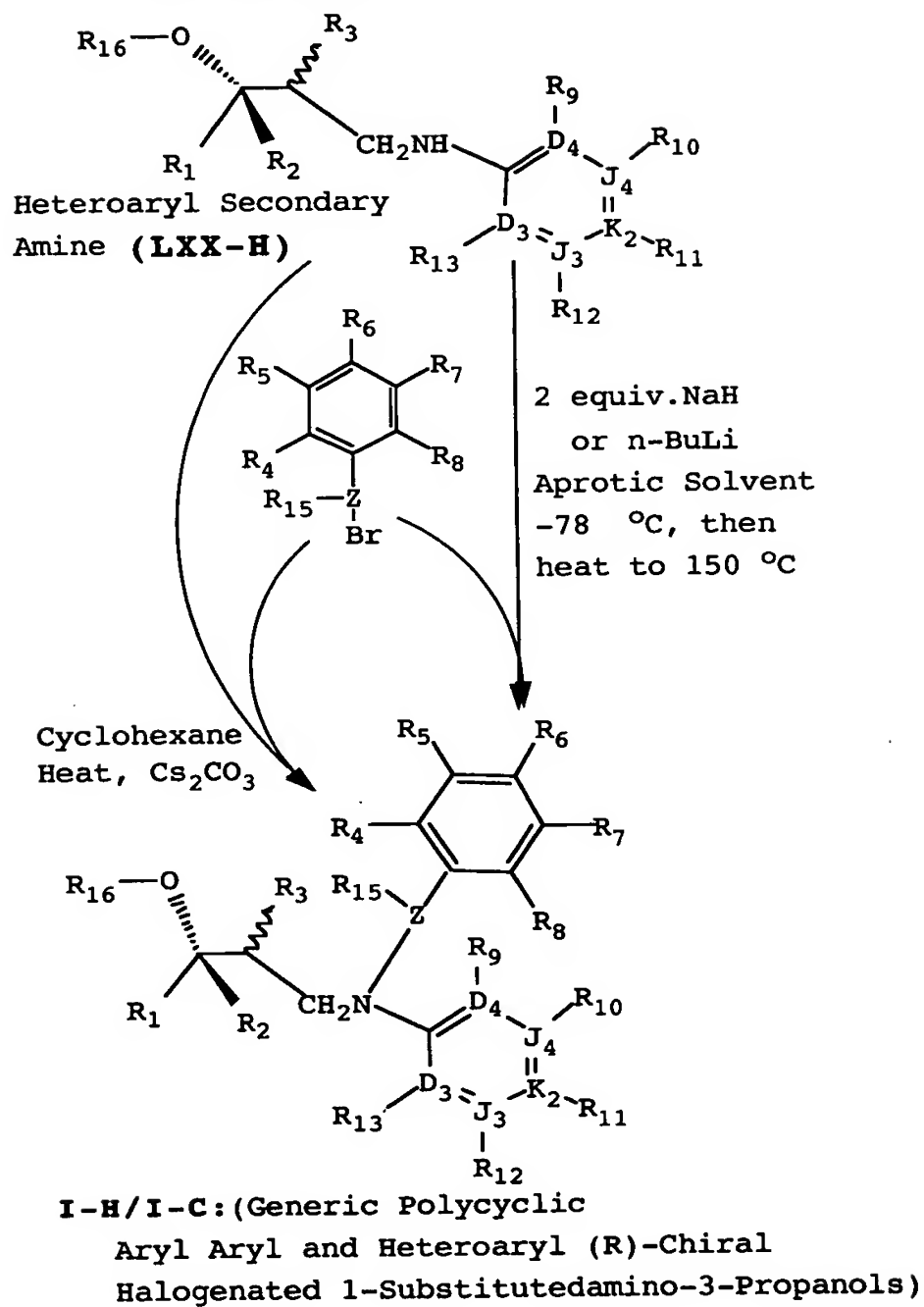
# Scheme 52



## Scheme 53



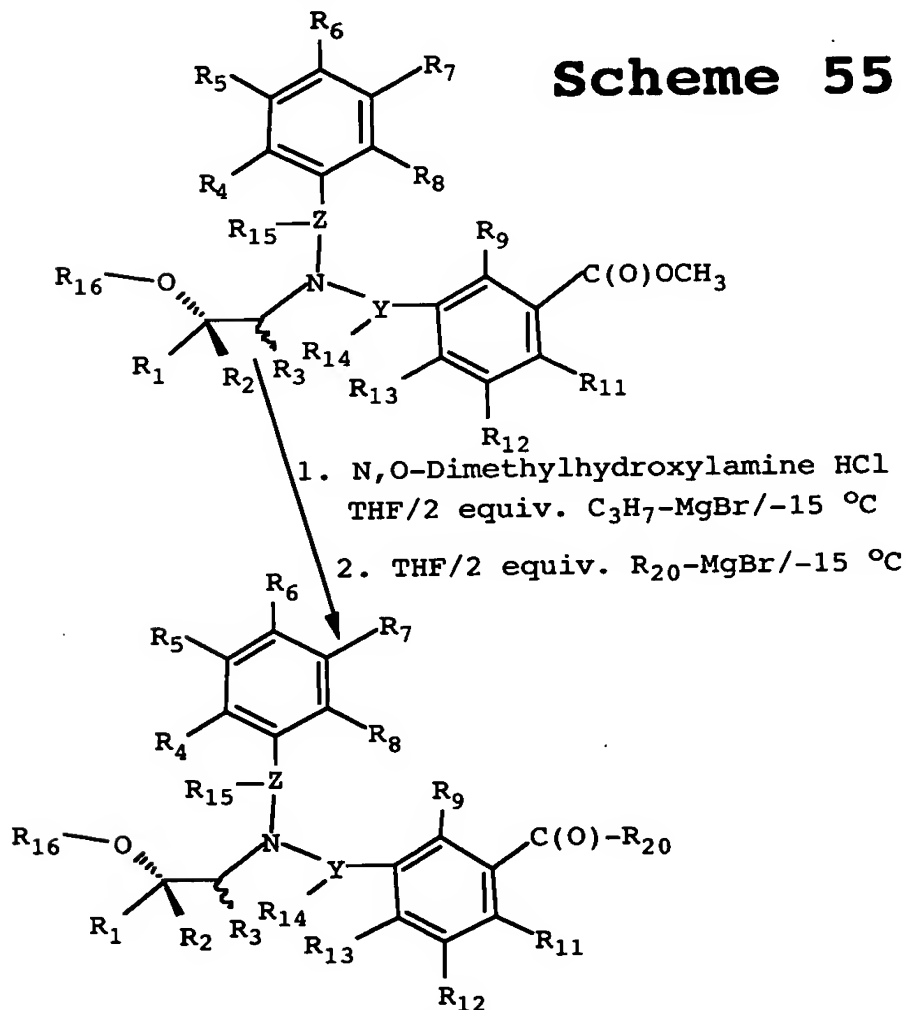
# Scheme 54





**I-CP:** (Polycyclic 3-Carbomethoxyphenyl Phenyl  
(R)-Chiral Halogenated 1-Substitutedamino-  
2-Propanols;  $R_{16} = H$ )

## Scheme 55

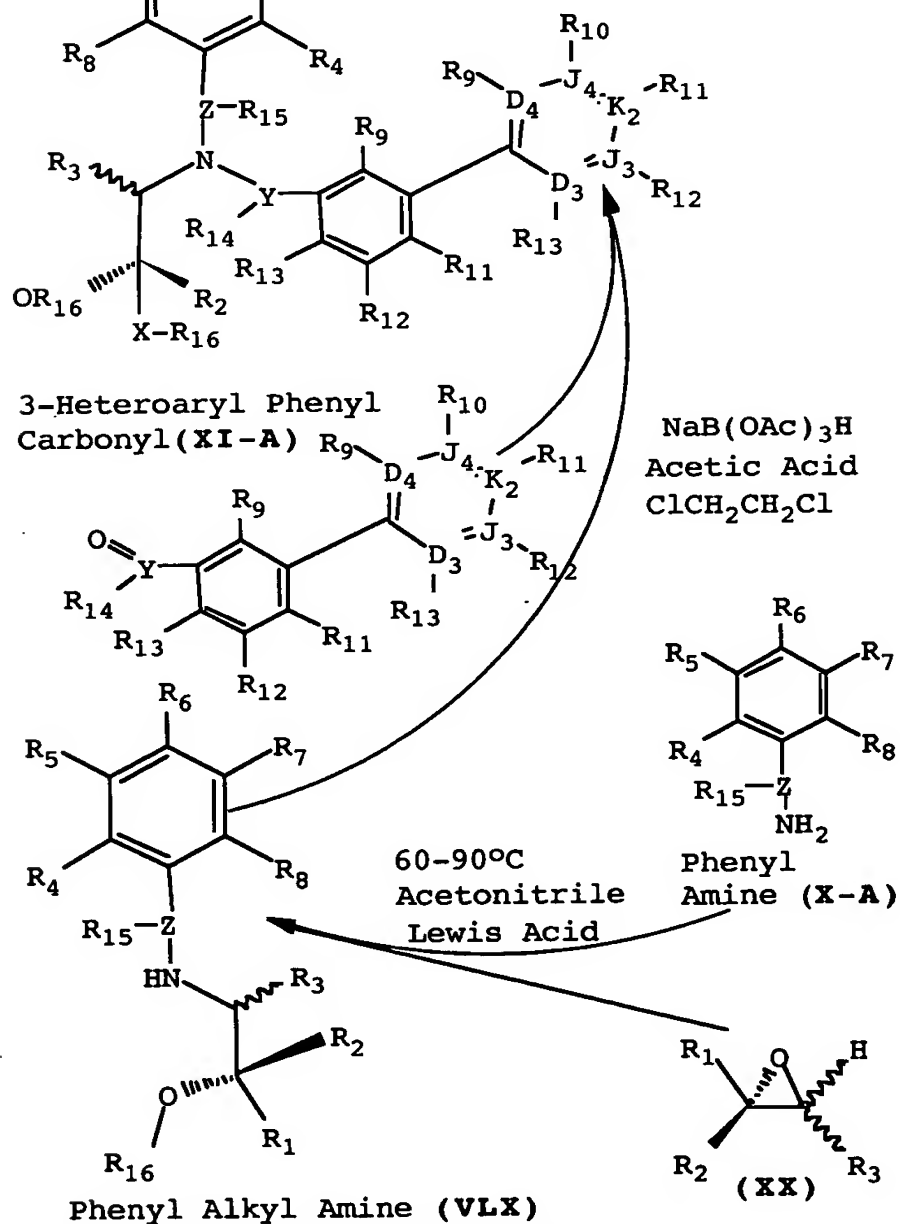


**I-CP:** (Polycyclic 3-( $R_{20}$ -carbonyl)phenyl Phenyl  
(R)-Chiral Halogenated 1-Substitutedamino-  
2-Propanols;  $R_{16} = H$ )

$R_{20}$  is selected from alkyl, alkenyl, alkynyl, aryl, aryloxyalkyl, aralkoxyalkyl, aralkylthioalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, heteroaralkylthioalkyl, cycloalkenylalkyl, arylthioalkyl, aralkyl, alkoxyalkyl, and cycloalkenyl.

**I-CP:** (Polycyclic 3-Heteroarylaryl Phenyl  
(R)-Chiral Halogenated 1-Substitutedamino-  
2-Propanols;  $R_{16} = H$ )

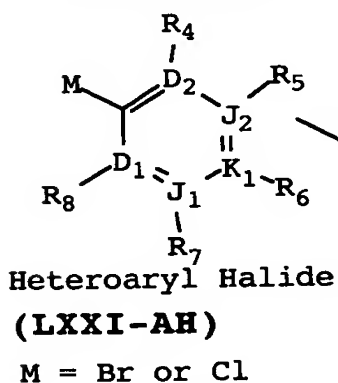
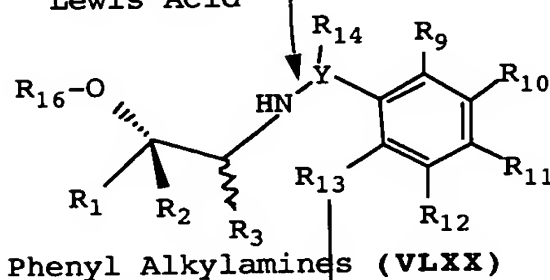
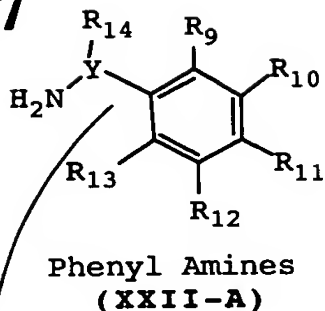
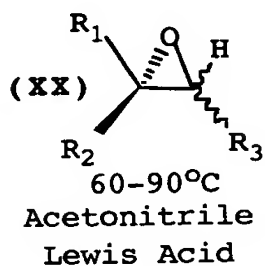
## Scheme 56



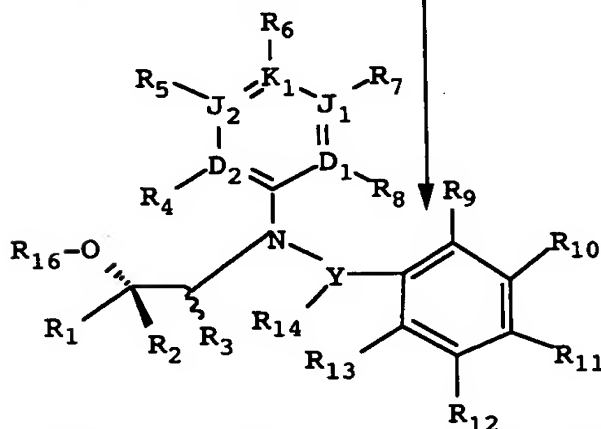
NOTE: Heteroaryl Analogs Can Be Prepared Using Heteroaryl Analogs of X-A, VLX, and XI-A.

# Scheme 57

## Method A:



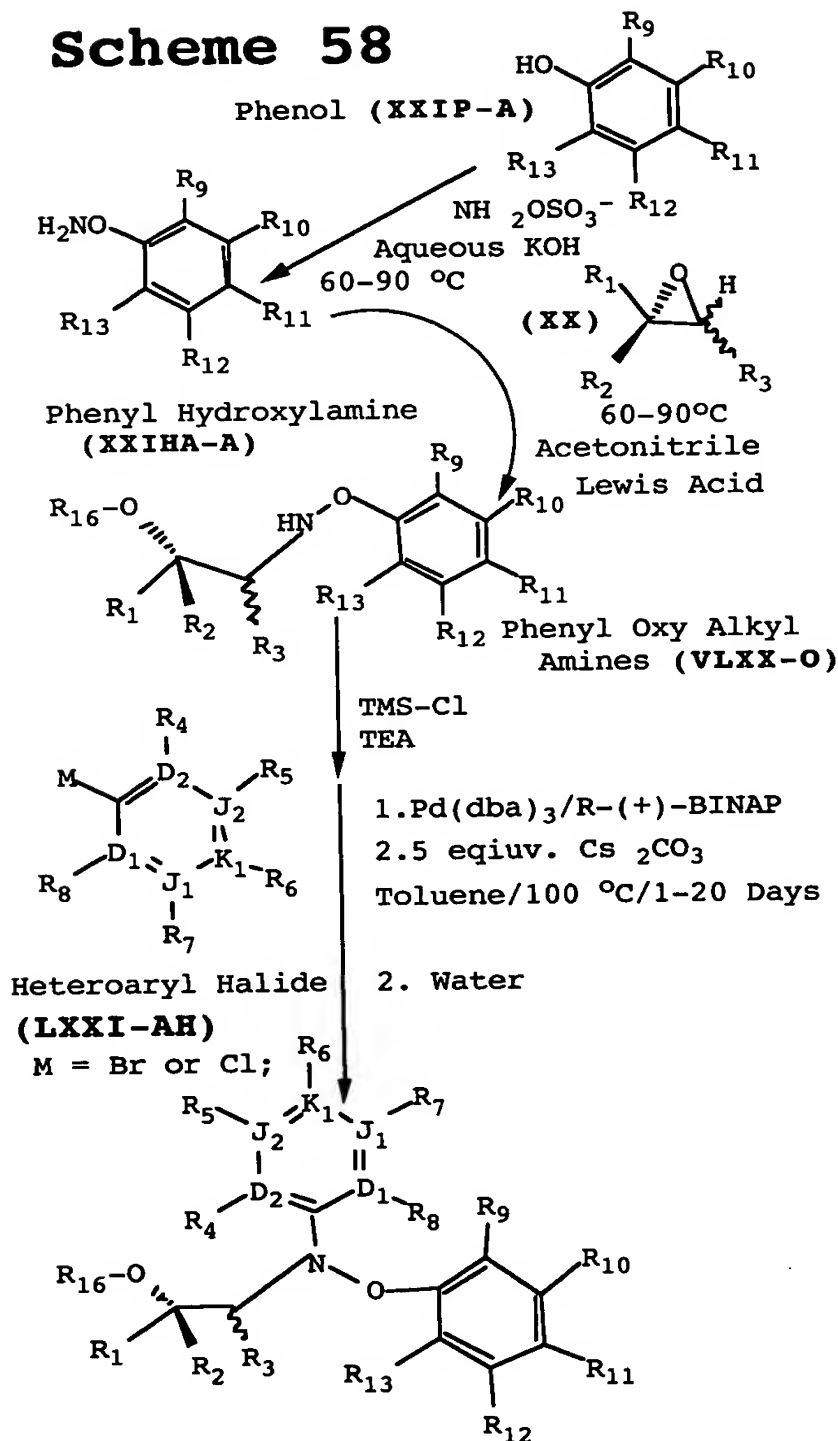
$\text{Pd}(\text{dba})_3/\text{R-(+)-BINAP}$   
2.5 equiv.  $\text{Cs}_2\text{CO}_3$   
Toluene  
100 °C/1-20 Days



**I-HPC:** Polycyclic Aryl-Heteroaryl (R)-Chiral  
Halogenated 1-Substitutedamino-2-Propanols  
when  $\text{R}_{16}$  equals H) NOTE: Aryl Analogs

(I-CP) of (I-HPC) Can Be Prepared by Starting  
With Aryl Bromide Analogs of (LXXI-AH).

# Scheme 58



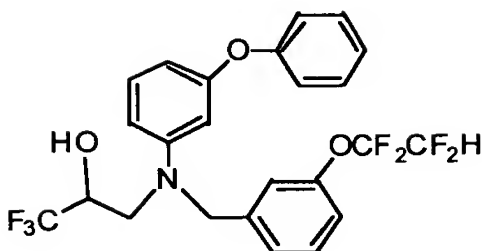
**I-HPC:** (Polycyclic Heteroaryl-Aryl Phenyl (R)-Chiral Halogenated 1-Substitutedamino-2-Propanols when R<sub>16</sub> = H and Y = O) NOTE: Diaryl (I-CP) and Diheteroaryl (I-HP) Analogs Can Be Prepared by Using Aryl Bromide and Heteroaryl-OH, respectively.

The following examples are provided to illustrate the present invention and are not intended to limit the scope thereof. Without further elaboration, it is believed that one skilled in the art can, using the preceding descriptions, utilize the present invention to its fullest extent. Therefore the following preferred specific embodiments are to be construed as merely illustrative and not limitative of the remainder of the disclosure in any way whatsoever. Compounds containing multiple variations of the structural modifications illustrated in the preceding schemes or the following Examples are also contemplated. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

One skilled in the art may use these generic methods to prepare the following specific examples, which have been or may be properly characterized by  $^1\text{H}$  NMR and mass spectrometry. These compounds also may be formed in vivo.

The following examples contain detailed descriptions of the methods of preparation of compounds of Formula V-H. These detailed descriptions fall within the scope and are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are Degrees centigrade unless otherwise indicated.

## EXAMPLE 1



5

**(2*R,S*)-3-[(3-phenoxyphenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol**

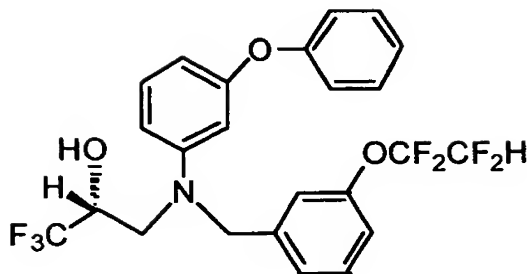
**EX-1A)** To a solution of 3-(1,1,2,2-tetrafluoroethoxy)toluene (50 g, 0.24 mol) and *N*-bromosuccinimide (42.75 g, 0.24 mol) in 100 mL of carbon tetrachloride under nitrogen was added 2,2'-azobisisobutyronitrile (0.71 g, 0.004 mol). The resultant mixture was refluxed for 2 h, then cooled to room temperature and quenched with 300 mL of water. The organic layer was collected, washed with water and brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo* to give 66.0 g (96%) of the desired crude 3-(1,1,2,2-tetrafluoroethoxy)bromomethylbenzene product as a yellow oil. <sup>1</sup>H NMR indicates that this oil is a mixture of products: 7% dibrominated, 67% monobrominated, and 20% starting material. The crude product was used without further purification. ESMS *m/z* = 287 [M+H]<sup>+</sup>.

**EX-1B)** The crude product (56 g, 0.14 mol) from **EX-1A** in 200 mL of cyclohexane was added dropwise under nitrogen to a solution of 3-phenoxyaniline (89 g, 0.480 mol) in 500 mL of cyclohexane. The reaction mixture was refluxed overnight, then cooled to room temperature and diluted with water and diethyl ether. The layers were separated, and the aqueous layer

was extracted with diethyl ether. The combined organic layers were dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to give a dark oil. The crude product was purified by column chromatography on silica gel eluting with 1:4 ethyl acetate in hexane to afford 44.96 g (83%) of the desired *N*-(3-phenoxyphenyl)-[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amine product as a yellow oil. ESMS  $m/z = 392 [\text{M}+\text{H}]^+$ .

To a mixture of the amine product (15.0 g, 0.038 mol) from EX-1B and 1,1,1-trifluoro-2,3-epoxypropane (8.58 g, 0.077 mol, TCI) was added a suspension of ytterbium (III) trifluoromethanesulfonate (2.37 g, 0.0031 mol) in 15 mL of acetonitrile. The resulting mixture was heated at 50 °C in a sealed glass vial for 1.5 h. The reaction mixture was cooled to room temperature then diluted with water and ethyl acetate and extracted. The organic layers were combined, dried over  $\text{MgSO}_4$ , and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 1:4 ethyl acetate in hexane to afford 12.03 g (62%) of the desired (2*RS*)-3-[(3-phenoxyphenyl)[[3-(1,1,2,2-tetrafluoroethoxy) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as a yellow oil. Anal. calcd. for  $\text{C}_{24}\text{H}_{20}\text{F}_7\text{NO}_3$ : C, 57.26; H, 4.00; N, 2.78. Found: C, 56.96; H, 4.35; N, 2.69. HRMS calcd. 504.1410  $[\text{M}+\text{H}]^+$ , found: 504.1431.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.28 (m, 4H), 7.14 (t, 1H), 7.07, (m, 3H), 7.00 (s, 1H), 6.94 (d, 2H), 6.46 (dd, 1H), 6.38 (dd, 1H), 6.35 (t, 1H), 5.84 (t, 1H), 4.60 (t, 2H), 4.36 (m, 1H), 3.82 (d, 1H), 3.48 (m, 1H), 2.51 (s, 1H).  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -79.0 (s, 3F), -88.21 (d, 2F), -137.05 (dd, 2F).

## EXAMPLE 2



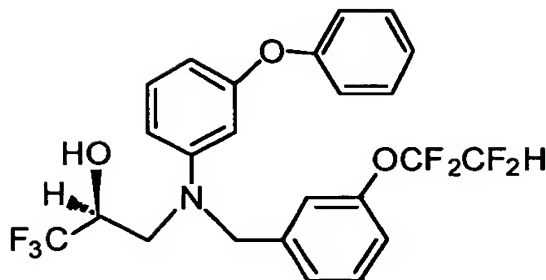
5

**(2R)-3-[(3-phenoxyphenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol**

On a Chiralpak AD HPLC column, (2RS)-3-[(3-phenoxyphenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol  
 10 (12.2 g, 0.024 mol) from EX-1 was purified by chiral chromatography to give 1.4 g (0.003 mol, 12%) of (2R)-3-[(3-phenoxyphenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl] amino]-1,1,1-trifluoro-2-propanol as a light yellow oil. Chiral purification was accomplished by eluting with 1:9 isopropanol  
 15 in heptane at 1.0 mL/min with 250 nm UV detection. The product eluted at 8.43 min.  $[\alpha]_{589} = +16.8.0$  (c 0.125 g/dL, CH<sub>3</sub>CN),  $[\alpha]_{365} = +84.0$  (c 0.125, CH<sub>3</sub>CN). Anal. calcd. for C<sub>24</sub>H<sub>20</sub>F<sub>7</sub>NO<sub>3</sub>: C, 57.26; H, 4.00; N, 2.78. Found: C, 56.96; H, 4.35; N, 2.69. HRMS calcd.: 504.1410 [M+H]<sup>+</sup>, found: 504.1388. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.28 (m, 4H), 7.14 (t, 1H), 7.07, (m, 3H), 7.00  
 20 (s, 1H), 6.94 (d, 2H), 6.46 (dd, 1H), 6.38 (dd, 1H), 6.35 (t, 1H), 5.84 (t, 1H), 4.60 (t, 2H), 4.36 (m, 1H), 3.82 (d, 1H), 3.48 (m, 1H), 2.51 (s, 1H). <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ -79.0 (s, 3F), -88.21 (d, 2F), -137.05 (dd, 2F).



## EXAMPLE 3

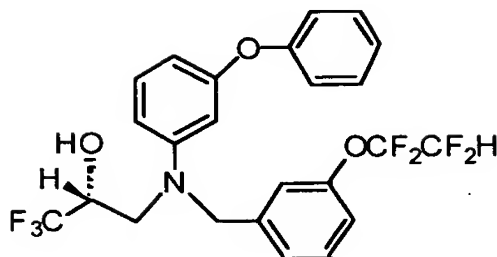


5

**(2S)-3-[(3-phenoxyphenyl)[[3-(1,1,2,2-tetrafluoroethoxy)-  
phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol**

On a Chiralpak AD HPLC column, (2*RS*)-3-[(3-phenoxyphenyl)[[3-(1,1,2,2-  
10 tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (12.2 g  
0.024 mol) from EX-1 was purified by chiral chromatography to give 10.5 g  
(0.021 mol, 86%) of (2*S*)-3-[(3-phenoxyphenyl)[[3-(1,1,2,2-  
tetrafluoroethoxy)phenyl] methyl]amino]-1,1,1-trifluoro-2-propanol as a light  
yellow oil. Chiral purification was accomplished by eluting with 1:9  
15 isopropanol in heptane at 1.0 mL/min with 250 nm UV detection. The product  
eluted at 6.36 min.  $[\alpha]_{589} = -17.0$  (c 0.265 g/dL, CH<sub>3</sub>CN),  $[\alpha]_{365} = -85.7$  (c  
0.265, CH<sub>3</sub>CN). Anal. calcd. For C<sub>24</sub>H<sub>20</sub>F<sub>7</sub>NO<sub>3</sub>: C, 57.26; H, 4.00; N, 2.78.  
Found: C, 56.96; H, 4.35; N, 2.69. HRMS calcd.: 504.1410 [M+H]<sup>+</sup>, found:  
504.1431. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.28 (m, 4H), 7.14 (t, 1H), 7.07, (m, 3H), 7.00  
20 (s, 1H), 6.94 (d, 2H), 6.46 (dd, 1H), 6.38 (dd, 1H), 6.35 (t, 1H), 5.84 (t, 1H),  
4.60 (t, 2H), 4.36 (m, 1H), 3.82 (d, 1H), 3.48 (m, 1H), 2.51 (s, 1H). <sup>19</sup>F NMR  
(CDCl<sub>3</sub>) δ -79.0 (s, 3F), -88.21 (d, 2F), -137.05 (dd, 2F).

## EXAMPLE 4



5

**(2R)-3-[(3-phenoxyphenyl)[[3-(1,1,2,2-tetrafluoroethoxy)-  
phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol**

Using a procedure adopted from H.C.Brown et al. (*J. Org. Chem.* **60**, 41-46, (1995)), *R*-(+)-1,1,1-trifluoro-2,3-epoxypropane was prepared beginning with the transfer of (+)-*B*-chlorodiisopinocampheylborane ((+)-DIP-Cl, 1.2 kg, 3.74 mol) to a 5 L three neck flask containing 5 L of ether under nitrogen. Anhydrous ether (5 L) was added, and the mixture was stirred until the solids dissolved and the temperature equilibrated to 0 °C. Then 3-bromotrifluoroacetone (326 mL, 3.14 mol) was added, and the reaction was stirred for 72 h while maintaining the temperature between -4 and +5 °C. The reaction was followed by <sup>19</sup>F NMR by removing an aliquot (20 μL), quenching with anhydrous methanol (0.6 mL), and referencing to external D<sub>2</sub>O. The reduction was 68 % complete after 48 h. The ether was removed under vacuum (100 torr to 0.1 torr), leaving a pale, viscous oil. A 5 L 3-neck flask equipped with stirrer, dropping funnel, and short-path distillation head with chilled receiver was charged with 50% (w/w) aqueous NaOH and heated to 40 °C. With external heat removed, the quenched reduction mixture was added dropwise to the aqueous NaOH, with the rate controlled to maintain the pot temperature below 65 °C. The product epoxide

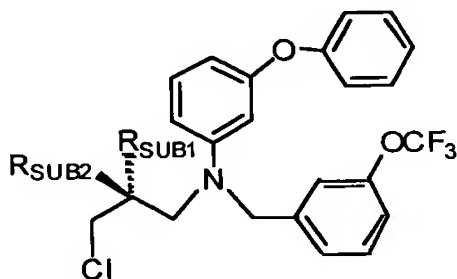
formed immediately, distilling over with a head temperature of 32-42 °C. A yellow-orange solid byproduct was broken up by stirring and some foaming was observed. When the distillation was complete, 145 g (43%) of the desired *R*-  
 5 (+)-1,1,1-trifluoro-2,3-epoxy-propane product was obtained as a clear, colorless oil.  $^1\text{H}$  NMR ( $\text{C}_6\text{D}_6$ )  $\delta$  2.50 (m, 1H,  $\text{CF}_3\text{CH}$ ), 2.15 (dd, 1H,  $J = 2.10, 5.01$  Hz), 1.75 (m, 1H).  $^{19}\text{F}$  NMR ( $\text{C}_6\text{D}_6$ )  $\delta$  -75.4 (d,  $J = 4.7$  Hz). Chiral GC/MS analysis was performed on the corresponding diethylamine adduct using a gamma cyclodextrin column (Supelco gammadex120 G-cyclodextrin fused silica):  
 10 4 drops of the epoxide, *R*-(+)-1,1,1-trifluoro-2,3-epoxypropane, and 4 drops of diethylamine were heated briefly in a sealed vial, cooled, diluted with methyl *t*-butyl ether, and analyzed. Found: two gc peaks: 10.97 min and 11.11 min (ratio 1:230; 99% ee), where the *R*-product predominated. MS calcd. for  $\text{C}_7\text{H}_{14}\text{F}_3\text{NO}$ :  $m/z = 186$   $[\text{M}+\text{H}]^+$ , found: 186, for both gc peaks. In contrast,  
 15 the diethylamine adduct obtained with the TCI trifluoromethyl-oxirane (lot OGH01) from EX-1, gave 2 peaks with identical MS signals  $m/z = 186$ , 10.96 min and 11.12 min (ratio 8.5:1; 79% ee), where the *S*-product predominated.

To a mixture *N*-(3-phenoxyphenyl)-[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]  
 20 methyl]-amine from EX-1B (1.48 g, 0.0038 mol) and *R*-(+)-1,1,1-trifluoro-2,3-epoxypropane (0.64 g, 0.0057 mol) was added a suspension of ytterbium (III) trifluoro-methanesulfonate (0.23 g, 0.0004 mol) in 1.5 mL of acetonitrile. The resulting mixture was heated at 50 °C in a sealed glass tube for 1.5 h. The reaction mixture was cooled to room temperature then diluted with water and  
 25 ethyl acetate and extracted. The organic layers were combined, dried over  $\text{MgSO}_4$ , and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 1:4 ethyl acetate in hexane to afford

1.2 g (63%) of the desired (2*R*)-3-[(3-phenoxyphenyl)-[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as a pure yellow oil (>96% ee by chiral HPLC analysis), which was identical in all  
5 respects to EX-2. Anal. calcd. for C<sub>24</sub>H<sub>20</sub>F<sub>7</sub>NO<sub>3</sub>: C, 57.26; H, 4.00; N, 2.78. found: C, 56.96; H, 4.35; N, 2.69. HRMS calcd.: 504.1410 [M+H]<sup>+</sup>, found: 504.1431. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.28 (m, 4H), 7.14 (t, 1H), 7.07, (m, 3H), 7.00 (s, 1H), 6.94 (d, 2H), 6.46 (dd, 1H), 6.38 (dd, 1H), 6.35 (t, 1H), 5.84 (t, 1H), 4.60 (t, 2H), 4.36 (m, 1H), 3.82 (d, 1H), 3.48 (m, 1H), 2.51 (s, 1H). <sup>19</sup>F NMR  
10 (CDCl<sub>3</sub>) δ -79.0 (s, 3F), -88.21 (d, 2F), -137.05 (dd, 2F).

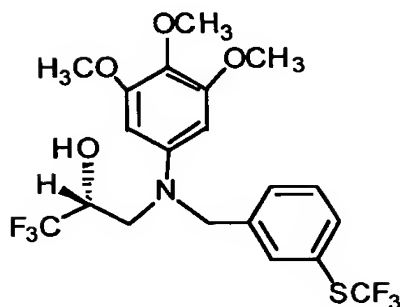
Additional examples can be prepared by one skilled in the art using similiar methods and commercially available epoxides. For example, 3-[(3-phenoxyphenyl)[[3-(trifluoromethoxy)phenyl]methyl]amino]-1-chloro-2-  
15 propanols can be prepared from the reaction of *N*-(3-phenoxyphenyl)-[[3-(trifluoromethoxy)phenyl]methyl]amine with either (*R*)-epichlorohydrin or (*S*)-epichlorohydrin, as illustrated in Example Table 1.

Example Table 1. 3-[(3-phenoxyphenyl)[[3-(trifluoromethoxy)phenyl]methyl]amino]-1-chloro-2-propanols.



<u>Ex.</u> <u>No.</u>	<u>R<sub>SUB1</sub></u>	<u>R<sub>SUB2</sub></u>	<u>Calculated</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>	<u>Observed</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>
5	OH	H	452.1240	452.1245
6	H	OH	452.1240	452.1259

## EXAMPLE 7



5

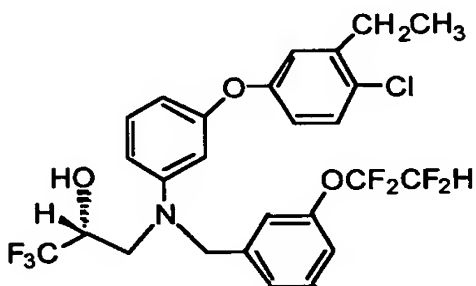
**(2*R*)-3-[(3,4,5-trimethoxyphenyl)[[3-(trifluoromethylthio)phenyl]methyl]-  
amino]-1,1,1-trifluoro-2-propanol**

**EX-45A)** To a 1,2-dichloroethane (12 mL) solution of 3,4,5-trimethoxyaniline  
 10 (0.80 g, 4.4 mmol) was added (3-trifluoromethylthio)benzaldehyde (0.90 g, 4.4  
 mmol), NaB(OAc)<sub>3</sub>H (1.20 g, 5.66 mmol) and acetic acid (0.26 mL, 4.5 mmol).  
 The cloudy solution was stirred at room temperature for 1 h. The reaction  
 mixture was poured into water and extracted with dichloromethane. The organic  
 layer was washed with saturated NaHCO<sub>3</sub> and brine, dried (MgSO<sub>4</sub>) and  
 15 evaporated to give 1.58 g (96%) of the desired *N*-(3,4,5-trimethoxyphenyl)[[3-  
 trifluoromethylthiophenyl]methyl]amine product as an off-white solid. MS: *m/z*  
 = 373.8 [M+H]<sup>+</sup>.

To an acetonitrile (3.2 mL) solution of amine (1.20 g, 3.2 mmol) from **EX-45A**  
 20 was added *R*-(+)-1,1,1-trifluoro-2,3-epoxypropane (0.55 mL, 6.4 mmol) from  
**EX-4** and Yb(OTf)<sub>3</sub> (0.40 g, 0.64 mmol). The cloudy solution was stirred in a  
 sealed flask at 50 °C for 18 h. The cooled reaction mixture was diluted with  
 diethyl ether and washed with water and brine. The organic layer was dried

(MgSO<sub>4</sub>) and evaporated to an oil. Purification by flash column chromatography on silica gel eluting with 20% ethyl acetate in hexane gave an oil which was triturated with hexanes to give a white solid. The precipitate was isolated by filtration and dried *in vacuo* to give 0.82 g (53 %) of the desired (2*R*)-  
 5 3-[(3,4,5-trimethoxyphenyl)[[3-(trifluoromethylthio)phenyl] methyl]-amino]-1,1,1-trifluoro-2-propanol product as a white solid, m.p. 88.9-89.1 °C (95% ee by chiral HPLC). Anal. calcd. for C<sub>20</sub>H<sub>21</sub>NO<sub>4</sub>SF<sub>6</sub>: C, 49.48; H, 4.36; N, 2.89. Found: C, 49.29; H, 4.21; N, 2.81. HRMS calcd.: 486.1174 [M+H]<sup>+</sup>, found: 486.1158. <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>) δ 3.10 (d, 1H), 3.18 (dd, 1H), 3.32 (s, 6H), 3.53 (d,  
 10 1H), 3.64 (s, 3H), 4.01 (m, 1H), 4.21 (dd, 2H), 5.70 (s, 2H), 6.80 (t, 1H), 6.94 (d, 1H), 7.23 (d, 1H), 7.37 (s, 1H). [α]<sub>589</sub> = +26.8 (c 1.099 g/dL, CHCl<sub>3</sub>).

### EXAMPLE 8



15

(2*R*)-3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol

20 **EX-8A)** To a solution of 1,3-dinitrobenzene (16.8 g, 0.1 mol) and 4-chloro-3-ethylphenol (15.6 g, 0.1 mol) in 200 mL of dimethylsulfoxide was added cesium carbonate (65 g, 0.2 mol). The reaction mixture was heated at 100 °C under nitrogen overnight then cooled to room temperature. The reaction mixture was

filtered through celite then rinsed with diethyl ether and a small amount of water. The filtrate was extracted several times with diethyl ether. The organic layers were combined, washed with water and brine, dried over  $\text{MgSO}_4$ , and concentrated *in vacuo* to give 21.8 g (78%) of the desired 3-(4-chloro-3-ethylphenoxy)-1-nitrobenzene product as a dark orange oil, which was greater than 90% pure by reverse phase HPLC analysis. HRMS calcd. for  $\text{C}_{14}\text{H}_{12}\text{ClNO}_3$ : 295.0849  $[\text{M}+\text{NH}_4]^+$ , found 295.0862.

**EX-8B)** To a solution of 3-(4-chloro-3-ethylphenoxy)-1-nitrobenzene (10 g, 0.036 mol) from **EX-8A** in 400 mL of glacial acetic acid and 1 mL of water was added zinc metal (20 g, 0.305 mol) at room temperature, and the resultant mixture was stirred for 1 h. The reaction mixture was filtered through celite. The filtrate was neutralized with ammonium hydroxide and extracted with diethyl ether. The organic layer was washed with water and brine, dried over  $\text{MgSO}_4$ , and concentrated *in vacuo* to give 10 g (100%) of the desired 3-(4-chloro-3-ethylphenoxy)aniline product as a dark orange oil, which was greater than 90% pure by reverse phase HPLC analysis. HRMS calcd. for  $\text{C}_{14}\text{H}_{14}\text{ClNO}$ : 248.0842  $[\text{M}+\text{H}]^+$ , found: 248.0833.

**EX-8C)** To a solution of 3-(4-chloro-3-ethylphenoxy)aniline (2.0 g, 8.1 mmol) from **EX-8B** and 3-(1,1,2,2-tetrafluoroethoxy)benzaldehyde (1.6 g, 7.3 mmol) in 30 mL of dichloroethane was added sodium triacetoxymethylborohydride (2.0 g, 9.7 mmol) and glacial acetic acid (0.51 mL, 8.9 mmol). The reaction mixture was stirred at room temperature for 1 h then quenched with water and extracted with diethyl ether. The organic layer was washed with water and brine, dried over  $\text{MgSO}_4$ , and concentrated *in vacuo* to give 3.5 g (95%) of the desired *N*-[(4-chloro-3-ethylphenoxy)phenyl]-3-[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-

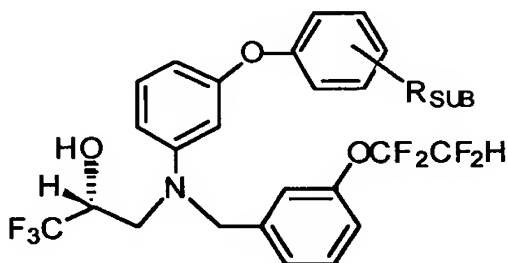


methyl]amine product as a brown oil, which was greater than 90% pure by reverse phase HPLC analysis. HRMS calcd. for  $C_{23}H_{20}ClF_4NO_2$ : 454.1197  $[M+H]^+$ , found: 454.1220.

- 5           A solution of *N*-[(4-chloro-3-ethylphenoxy)phenyl]-3-[[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amine (1.8 g, 4.0 mmol) from EX-8C, *R*-(+)-1,1,1-trifluoro-2,3-epoxy-propane (0.64 g, 0.0057 mol) from EX-4, and ytterbium (III) trifluoromethanesulfonate (0.25 g, 0.4 mmol) in 1.5 mL of acetonitrile was heated at 40 °C in a sealed glass tube for 1 h. The reaction
- 10           mixture was cooled to room temperature then diluted with water and diethyl ether and extracted. The ether layer was washed with water and brine, dried over  $MgSO_4$ , and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 1:7:0.01 of ethyl acetate:hexane:ammonium hydroxide to afford 1.5 g (66%) of the desired (2*R*)-3-
- 15           [[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-tri-fluoro-2-propanol product as a yellow oil (96% ee by chiral HPLC analysis).  $[\alpha]_{589}^{25} = +36.9$  (c 1.044g%,  $CHCl_3$ ),  $[\alpha]_{365}^{25} = +189.7$  (c 1.044g%,  $CHCl_3$ ). The refractive index @ 25 °C is 1.5275. Anal. calcd. for  $C_{26}H_{23}ClF_7NO_3$ : C, 55.18; H, 4.10; N, 2.48. found: C, 54.92; H, 4.05; N,
- 20           2.33. HRMS calcd.: 566.1330  $[M+H]^+$ , found: 566.1323.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.30 (t, 1H), 7.20 (d, 1H), 7.15 (t, 1H), 7.08 (t, 2H), 7.00 (s, 1H), 6.86 (d, 1H), 6.68 (dd, 1H), 6.48 (dd, 1H), 6.36 (dd, 1H), 6.34 (t, 1H), 5.81 (tt, 1H), 4.62 (s, 2H), 4.32 (m, 1H), 3.84 (dd, 1H), 3.55 (dd, 1H), 2.67 (q, 2H), 2.45 (bs, 1H), 1.17 (t, 3H).  $^{19}F$  NMR ( $CDCl_3$ )  $\delta$  -79.22 (d, 3F), -88.57 (m, 2F), -137.16 (dt,
- 25           2F).

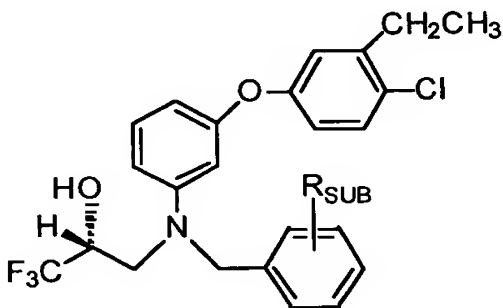
Additional examples of (2*R*)-3-[[3-(substituted-phenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols and (2*R*)-3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[3-substituted-phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanols can be prepared by one skilled in the art using similar methods, as shown in Example Tables 2 and 3, respectively.

Example Table 2. (2*R*)-3-[[3-(Substituted-phenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols.



<u>Ex.</u> <u>No.</u>	<u>R<sub>SUB</sub></u>	<u>Calculated</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>	<u>Observed</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>
9	4-methyl	518.1566	518.1587
10	3-isopropyl	546.1879	546.1900
11	3-ethyl	532.1723	532.1713

Example Table 3. (2*R*)-3-[[3-(4-Chloro-3-ethylphenoxy)phenyl][[3-substituted-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols.



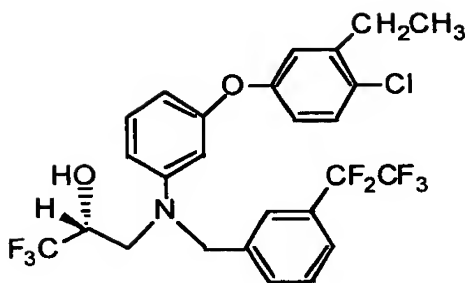
5

<u>Ex.</u> <u>No.</u>	<u>R<sub>SUB</sub></u>	<u>Calculated</u>	<u>Observed</u>
		<u>Mass</u> <u>[M+H]<sup>+</sup></u>	<u>Mass</u> <u>[M+H]<sup>+</sup></u>
12	3-trifluoromethoxy	534.1271	534.1309
13	3-trifluoromethyl, 4-fluoro	536.1228	536.1265
14	2-fluoro, 4-trifluoromethyl	536.1228	536.1241
15	2-trifluoromethyl, 4-fluoro	536.1228	536.1245
16	2-fluoro, 5-trifluoromethyl	536.1228	536.1252
17	2-fluoro, 6-trifluoromethyl	536.1228	536.1199

10

15

## EXAMPLE 18



5

(2R)-3-[[[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(1,1,1,2,2-pentafluoroethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol

EX-18A) Sodium pentafluoroethyl propionate (8.4 g, 50 mmol) and 3-iodotoluene (5.5 g, 25 mmol) were dissolved in anhydrous DMF (300 mL) under nitrogen. CuI (9.5 g, 50 mmol) was added, and the mixture was heated to 160 °C under nitrogen for 4 h, at which time a 15 mL fraction of a mixture of DMF and 3-pentafluoroethyl toluene was collected. The distillate was diluted with Et<sub>2</sub>O and was washed with brine. The ether layer was dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to give 5.25 g (55%) of the desired 3-pentafluoroethyl-toluene product as a colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.36 (m, 4H), 2.40 (s, 3H). <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ -85.2 (s, 3F), -115.2 (s, 2F).

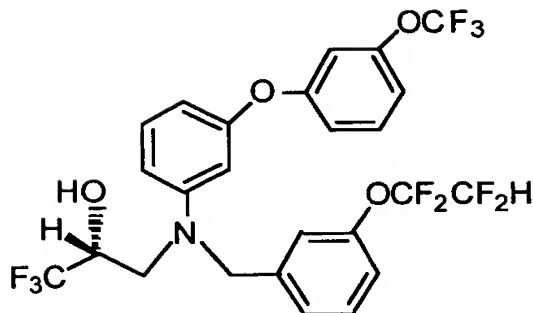
EX-18B) The 3-pentafluoroethyl-toluene (2.9 g, 13.8 mmol) product from EX-18A and N-bromosuccinimide (2.5 g, 13.8 mmol) were dissolved in CCl<sub>4</sub> (25 mL). AIBN (50 mg, 0.3 mmol) was added, and the mixture was refluxed for 3.5 h under N<sub>2</sub>. The reaction mixture was cooled to room temperature and diluted with water. The layers were separated, and the organic layer was washed with

brine, dried with anhydrous  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo* to give 3.4 g (87%) of a colorless oil. The  $^1\text{H}$  NMR spectrum indicated that the crude product contained 3-pentafluoroethyl-benzylbromide (70%), the benzyldibromide (10%) and pentafluoroethyl toluene (20%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.60 (m, 2H), 7.50 (m, 2H), 4.50 (s, 2H).  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -85.1 (s, 3F), -115.4 (s, 2F).

**EX-18C)** A solution of 3-(4-chloro-3-ethylphenoxy)aniline (1.7 g, 6.9 mmol) was prepared in cyclohexane (13 mL). A solution of crude 3-pentafluoroethyl benzylbromide (1 g, 3.5 mmol) product from **EX-18B** in cyclohexane (10 mL) was added dropwise under nitrogen over 3 min. The reaction mixture was refluxed under  $\text{N}_2$  for 24 h and then was cooled to room temperature. The mixture was diluted with  $\text{Et}_2\text{O}$  and saturated aqueous  $\text{NaHCO}_3$ . The layers were separated, and the aqueous layer was extracted with  $\text{Et}_2\text{O}$ . The organic layer was washed with brine, dried with anhydrous  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluting with hexanes in ethyl acetate (95:5) which gave 0.56 g (35%) of the desired *N*-[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(pentafluoro-ethyl)phenyl]-methyl]amine product as a brown oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.53 (m, 4H), 7.27 (d, 1H), 7.15 (t, 1H), 6.93 (d, 1H), 6.77 (dd, 1H), 6.41 (tt, 2H), 6.30 (t, 1H), 4.41 (s, 2H), 2.73 (q, 2H), 1.23 (t, 3H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  158.6, 156.1, 143.4, 141.3, 140.2, 131.3, 130.7, 130.4, 129.4, 128.1, 120.4, 117.8, 108.8, 103.9, 48.5, 27.5, 14.1.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -85.1 (s, 3F), -115.2 (s, 2F). HRMS calcd. for  $\text{C}_{23}\text{H}_{19}\text{ClF}_5\text{NO}$ : 456.1154  $[\text{M}+\text{H}]^+$ , found: 456.1164.

The *N*-[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(pentafluoroethyl)phenyl]-methyl]amine (0.4 g, 0.88 mmol) product of EX-18C was dissolved in anhydrous acetonitrile (1.5 mL). *R*-(+)-1,1,1-trifluoro-2,3-epoxypropane (0.22 g, 1.94 mmol) and Yb(OTf)<sub>3</sub> (22 mg, 0.035 mmol) were added, and the reaction mixture was stirred under N<sub>2</sub> at 45 °C in a sealed glass tube for 15 h. The reaction mixture was then cooled to room temperature and diluted with Et<sub>2</sub>O and saturated aqueous NaHCO<sub>3</sub>. The layers were separated and the aqueous layer was extracted with Et<sub>2</sub>O. The ether layers were combined, washed with brine, dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The viscous oil was adsorbed onto silica gel and purified by column chromatography eluting with hexanes in ethyl acetate (95:5) which gave 0.32 g (64%) of the desired (2*R*)-3-[(4-chloro-3-ethylphenoxy)phenyl][[3-(pentafluoroethyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as a viscous, colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.47 (m, 4H), 7.23 (m, 3H), 6.90 (d, 1H), 6.72 (dd, 1H), 6.52 (d, 1H), 6.42 (m, 2H), 4.73 (s, 2H), 4.39 (m, 1H), 3.91 (dd, 1H), 3.58 (m, 2H), 2.73 (q, 2H), 2.57 (s, 1H), 1.22 (t, 3H). <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ -79.2 (s, 3F), -84.9 (s, 3F), -115.2 (s, 2F). HRMS calcd. for C<sub>26</sub>H<sub>22</sub>ClF<sub>8</sub>NO<sub>2</sub>: 568.1290 [M+H]<sup>+</sup>, found: 568.1296.

## EXAMPLE 19



5

(2*R*)-3-[[3-(3-trifluoromethoxyphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol

**EX-19A)** To a solution of 1,3-dinitrobenzene (4.5 g, 0.03 mol) and 3-trifluoromethoxy-phenol (4.8 g, 0.03 mol) in 54 mL of dimethylsulfoxide was added cesium carbonate (21.8 g, 0.07 mol). The reaction mixture was heated at 100 °C under nitrogen overnight then cooled to room temperature. The reaction mixture was diluted with water and extracted with diethyl ether several times. The organic layers were combined, washed with 1 N HCl and water, dried over

15  $\text{MgSO}_4$ , and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate in hexane to afford 3.0 g (38%) of the desired 3-(3-trifluoro-methoxyphenoxy)nitrobenzene product as a yellow-orange liquid which was 85% pure by reverse phase HPLC analysis. This material was carried on without further purification.

20

**EX-19B)** To a solution of 3-(3-trifluoromethoxyphenoxy)nitrobenzene (3.0 g, 0.01 mol) from **EX-19A** in 100 mL of glacial acetic acid was added zinc metal (6.6 g, 0.1 mol) at room temperature, and the resultant mixture was stirred for 1 h. The reaction mixture was filtered through celite. The filtrate was neutralized

with ammonium hydroxide and extracted with diethyl ether then ethyl acetate.

The combined organic layers were dried over  $\text{MgSO}_4$  and concentrated *in vacuo*.

The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate in hexane to afford 1.2 g (44%) of the desired 3-(3-

5 trifluoromethoxyphenoxy)aniline product as a yellow oil which was 98% pure by reverse phase HPLC analysis. Anal. calcd. for  $\text{C}_{13}\text{H}_{10}\text{F}_3\text{NO}_2$ : C, 58.00; H, 3.74; N, 5.20. found: C, 57.68; H, 3.57; N, 5.14. HRMS calcd.: 270.0742  $[\text{M}+\text{H}]^+$ , found: 270.0767.

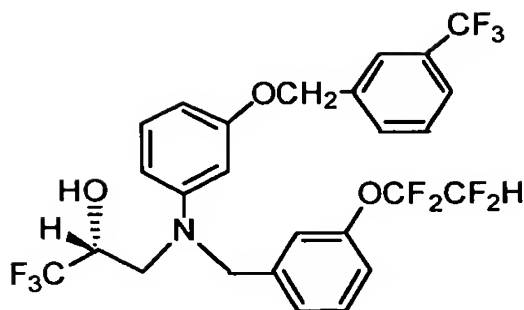
10 **EX-19C)** To a solution of 3-(3-trifluoromethoxyphenoxy)aniline (1.0 g, 3.7 mmol) from **EX-19B** and 3-(1,1,2,2-tetrafluoroethoxy)benzaldehyde (0.83 g, 3.7 mmol) in 18.5 mL of dichloroethane was added sodium triacetoxyborohydride (1.0 g, 4.7 mmol) and glacial acetic acid (0.25 mL, 4.3 mmol). The reaction mixture was stirred at room temperature overnight then quenched with saturated  
15 aqueous sodium bicarbonate and extracted with methylene chloride. The organic layer was dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to give 1.8 g (100%) of the desired [3-(3-trifluoromethoxy-phenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl] amine product as a yellow oil, which was greater than 90% pure by reverse phase HPLC analysis. HRMS calcd. for  $\text{C}_{22}\text{H}_{16}\text{F}_7\text{NO}_3$ :  
20 476.1097  $[\text{M}+\text{H}]^+$ , found: 476.1069. This material was carried on to the next step without further purification.

A solution of [3-(3-trifluoromethoxyphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amine (1.8 g, 3.7 mmol) from **EX-19C**, *R*-(+)-  
25 1,1,1-trifluoro-2,3-epoxy-propane (0.57 g, 5.2 mmol), and ytterbium (III) trifluoromethanesulfonate (0.24 g, 0.38 mmol) in 2.0 mL of acetonitrile was



heated at 40 °C in a sealed glass tube overnight. At this time reverse phase  
 HPLC analysis indicated that the reaction was only 50% complete. Additional  
 ytterbium (III) trifluoromethanesulfonate and *R*-(+)-1,1,1-trifluoro-2,3-  
 5 epoxypropane (0.26 g, 2.3 mmol) were added to the reaction mixture and again  
 heated at 40 °C in a sealed glass tube for 48 h. The reaction mixture was cooled  
 to room temperature then diluted with water and methylene chloride and  
 extracted. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, and  
 concentrated *in vacuo*. The crude product was purified by reverse phase HPLC  
 10 eluting with 30% to 90% acetonitrile in water to afford 1.25 g (23%) of the  
 desired (2*R*)-3-[[3-(3-trifluoromethoxyphenoxy) phenyl][3-(1,1,2,2-  
 tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as  
 yellow-brown oil (90% ee by chiral HPLC analysis). HRMS calcd. for  
 C<sub>25</sub>H<sub>19</sub>F<sub>10</sub>NO<sub>4</sub>: 588.1233 [M+H]<sup>+</sup>, found: 588.1225. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ  
 15 7.35-7.18 (m, 3H), 7.12 (t, 2H), 7.01 (s, 1H), 6.93 (d, 1H), 6.85 (d, 1H), 6.82 (s,  
 1H), 6.56 (dd, 1H), 6.47 (dd, 1H), 6.41 (s, 1H), 5.88 (t, 1H), 4.66 (s, 2H), 4.35  
 (m, 1H), 3.86 (d, 1H), 3.59 (dd, 1H), 2.02 (s, 1H). <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ -58.31  
 (s, 3F), -79.24 (d, 3F), -88.57 (m, 2F), -137.16 (dt, 2F).

## EXAMPLE 20



**(2R)-3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[(trifluoromethyl)-phenyl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol**

- 10 **EX-20A)** To a solution of 3-aminophenol (4.91 g, 45.0 mmol) and 3-(1,1,2,2-tetrafluoroethoxy)benzaldehyde (10.0 g, 45.0 mmol) in 100 mL of 1,2-dichloroethane was added sodium triacetoxyborohydride (14.28 g 67.5 mmol) and glacial acetic acid (2.7 mL, 47.3 mmol). The reaction mixture was stirred at room temperature for 6 h then quenched with water and extracted with
- 15 dichloromethane. The organic layer was washed with saturated aqueous sodium bicarbonate, dried over  $\text{MgSO}_4$ , and concentrated *in vacuo* to give 11.82 g (83%) of the desired 3-[[[3-(1,1,2,2-tetrafluoro-ethoxy)phenyl]methyl]amino]phenol product as a dark orange oil.  $^1\text{H}$  NMR (acetone- $d_6$ )  $\delta$  7.01-7.38 (m, 5H), 6.26-6.44 (m, 3H), 6.08 (t, 1H), 5.88 (tt, 1H), 4.34 (s, 2H).

20

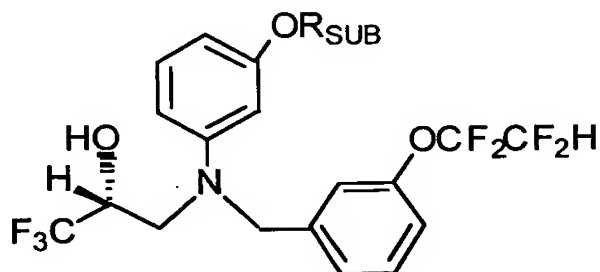
**EX-20B)** A solution of 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]phenol (5.1 g, 16.2 mmol) from **EX-20A**, *R*-(+)-1,1,1-trifluoro-2,3-epoxypropane (1.5 mL, 17.4 mmol), and ytterbium trifluoromethanesulfonate

(1.0 g, 10 mol%) in 10 mL of acetonitrile was heated at 50 °C in a sealed glass tube for 4 h. The reaction mixture was cooled to room temperature, then diluted with water and diethyl ether and extracted. The ether layer was washed with  
 5 saturated aqueous sodium bicarbonate and brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo* to give 5.64 g (81%) of the desired (2*R*)-3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3,3,3-trifluoro-2-hydroxy-propyl)amino]-phenol product as a yellow oil. <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 7.41 (t, 1H), 7.23 (d, 1H), 7.16-7.20 (m, 2H), 6.97 (t, 1H), 6.42 (tt, 1H), 6.18-6.24 (m, 3H), 4.77 (s,  
 10 2H), 4.43-4.48 (m, 1H), 3.58 (dd, 1H), 3.39 (dd, 1H).

To a solution of (2*R*)-3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3,3,3-trifluoro-2-hydroxypropyl)amino]phenol (100 mg, 0.23 mmol) from EX-20B and 3-trifluoromethylbenzyl bromide (70.0 mg, 0.27 mmol) in 2.5 mL of acetone  
 15 was added cesium carbonate (100 mg, 0.31 mmol). The reaction mixture was heated at 60 °C for 18 h then cooled to room temperature. The reaction mixture was filtered through celite, and the filtrate was concentrated. The residue was purified by reverse phase HPLC eluting with 50% to 90% acetonitrile in water to afford 63.3 mg (45%) of the desired (2*R*)-3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[[3-(trifluoro-methyl)phenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol product as an orange oil.  
 20 HRMS calcd. for C<sub>26</sub>H<sub>21</sub>F<sub>10</sub>NO<sub>3</sub>: 586.1440 [M+H]<sup>+</sup>, found: 586.1419. <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 7.61-7.82 (m, 4H), 7.41 (t, 1H), 7.25 (d, 1H), 7.10-7.21 (m, 3H), 6.34-6.67 (m, 4H), 5.73 (d, 1H), 5.19 (s, 2H), 4.82 (s, 2H), 4.34-4.48  
 25 (m, 1H), 3.99 (dd, 1H), 3.68 (dd, 1H).

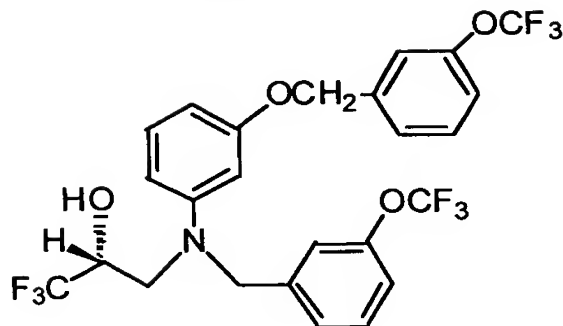
Additional examples of (2*R*)-3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]-[3-[[aryl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in. Example Table 4.

Example Table 4. (2*R*)-3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[[aryl]methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanols.



<u>Ex.</u> <u>No.</u>	<u>R<sub>SUB</sub></u>	<u>Calculated</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>	<u>Observed</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>
21	3,5-difluorobenzyl	554.1378	554.1352
22	3-trifluoromethoxybenzyl	602.1389	602.1390
23	3-isopropyl	470.1566	464.1601

## EXAMPLE 24



5           **(2R)-3-[[[3-[[3-(trifluoromethoxy)phenyl]methoxy]phenyl][[3-(trifluoromethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol**

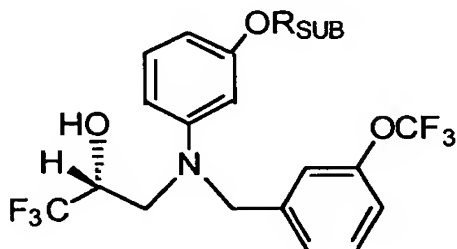
(2R)-3-[[[3-[[3-(trifluoromethoxy)phenyl]methoxy]phenyl][[3-(trifluoro-  
methoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol can be prepared by  
10 one skilled in the art using similar methods starting from 3-(trifluoromethoxy)-benzaldehyde. HRMS calcd. for  $C_{25}H_{20}F_9NO_4$ : 570.1327  $[M+H]^+$ , found: 570.1325.  $^1H$  NMR (acetone- $d_6$ )  $\delta$  7.43 (t, 1H), 7.32 (d, 1H), 7.18-7.23 (m, 2H), 7.01-7.16 (m, 3H), 6.92-7.00 (m, 1H), 6.38-6.45 (m, 3H), 5.12 (s, 2H), 4.81 (s, 2H), 4.41-4.53 (m, 1H), 3.98 (dd, 1H), 3.63 (dd, 1H).

15

Additional examples of (2R)-3-[[[3-[[aryl]methoxy]phenyl][[3-(trifluoromethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols can be prepared by one skilled in the art using similar methods, as shown in Example Table 5.

20

Example Table 5. (2*R*)- 3-[[3-[[aryl]methoxy]phenyl][[3-(trifluoromethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols.



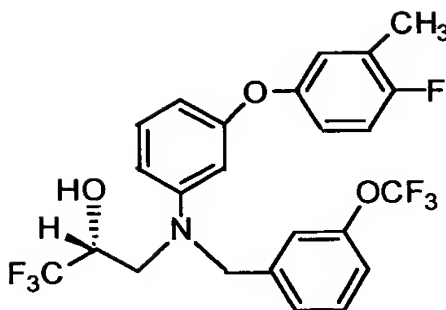
5

<u>Ex.</u> <u>No.</u>	<u>R<sub>SUB</sub></u>	<u>Calculated</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>	<u>Observed</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>
25	4-trifluoromethoxybenzyl	570.1327	570.1299
26	3,5- di(trifluoromethyl)benzyl	622.1252	622.1252
27	3-trifluoromethylbenzyl	554.1378	554.1369
28	3,5-difluorobenzyl	522.1315	522.1259
29	benzyl	486.1504	486.1504
30	isopropyl	438.1504	438.1509
31	cyclohexylmethyl	492.1973	492.1973
32	cyclopentyl	464.1660	464.1641

10

15

## EXAMPLE 33



5

**(2R)-3-[[[3-(4-fluoro-3-methylphenoxy)phenyl][[3-(trifluoromethoxy)-  
phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol**

**EX-33A)** To a solution of 3-bromoaniline (5.7 mL, 52.6 mmol) and 3-trifluoro-  
methoxybenzaldehyde (10.0 g, 52.6 mmol) in 135 mL of dichloroethane was  
added sodium triacetoxyborohydride (14.5 g, 68.4 mmol) and glacial acetic acid  
(3.1 mL, 54.7 mmol). The reaction was stirred at room temperature for 2 h, then  
quenched with water and extracted with dichloromethane. The organic layer was  
washed with saturated aqueous sodium bicarbonate, dried over  $\text{MgSO}_4$ , and  
concentrated *in vacuo*. The crude product was purified by column  
chromatography on silica gel eluting with 1:9 ethyl acetate in hexane to give 14.3  
g (78%) of the desired of *N*-(3-bromophenyl)[[3-(trifluoromethoxy)  
phenyl]methyl]amine product as a dark brown oil. HRMS calcd. for  
 $\text{C}_{14}\text{H}_{11}\text{BrF}_3\text{NO}$ : 346.0055  $[\text{M}+\text{H}]^+$ , found: 346.0052.

20

**EX-33B)** A solution of of *N*-(3-bromophenyl)[[3-(trifluoromethoxy)phenyl]methyl]-amine (10.0 g, 28.9 mmol) from EX-33A, *R*-(+)-1,1,1-trifluoro-2,3-epoxypropane (4.2 g, 37.6 mmol), and ytterbium (III)

trifluoromethanesulfonate (1.79 g, 2.89 mmol) in 27 mL of acetonitrile was heated at 50 °C in a sealed glass tube overnight. The reaction mixture was cooled to room temperature and filtered through celite. The crude product was purified by column chromatography on silica gel eluting with 2:3 dichloromethane in hexane to afford 11.9 g (90%) of the desired (2*R*)-3-[[3-bromophenyl]][3-(tri-fluoromethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as a brown oil (98% ee by chiral HPLC analysis). HRMS calcd. for C<sub>17</sub>H<sub>14</sub>BrF<sub>6</sub>NO<sub>2</sub>: 458.0190 [M+H]<sup>+</sup>, found: 458.0197.

10

A suspension of 4-fluoro-3-methylphenol (98.0 μL, 0.88 mmol) and cesium carbonate (319.5 mg, 0.98 mmol) in 1 mL of *N,N*-dimethylacetamide was preheated at 60 °C for 5 minutes. To this solution was added 4 mL of a stock solution containing (2*R*)-3-[[3-bromophenyl]][3-(trifluoromethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (200 mg, 0.437 mmol) from EX-33B, 1-naphthoic acid (164 mg, 0.95 mmol), copper(I) trifluoromethanesulfonate benzene complex (21.8 mg, 0.0434 mmol), 4 Å sieves (105 mg), and 4 mL of toluene. The reaction mixture was stirred at 105 °C for 3 weeks and 2 days. During that time, additional cesium carbonate and catalyst were added (a spatula tip of each) to the reaction three different times. The reaction was cooled to room temperature, filtered through celite, and the solvent was evaporated. The residue was purified by reverse phase HPLC eluting with 35% to 90% acetonitrile in water to afford 50.5 mg (23%) of the desired (2*R*)-3-[[3-(4-fluoro-3-methylphenoxy)phenyl]][3-(trifluoromethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as an orange oil. HRMS calcd. for C<sub>24</sub>H<sub>20</sub>F<sub>7</sub>NO<sub>3</sub>: 504.1410 [M+H]<sup>+</sup>, found: 504.1389. <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 7.44 (t, 1H), 7.24 (d, 1H), 7.08-7.21 (m, 3H), 6.98 (t, 1H), 6.75-6.85 (m, 1H), 6.68-6.74 (m,

20

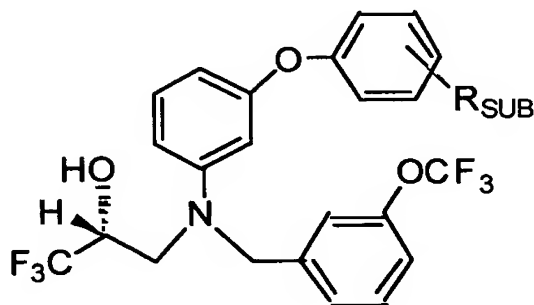
25



1H), 6.53 (d, 1H), 6.21-6.34 (m, 2H), 4.79 (t, 2H), 4.46-4.53 (m, 1H), 3.95 (dd, 1H), 2.61-2.72 (m, 1H), 2.20 (s, 3H).

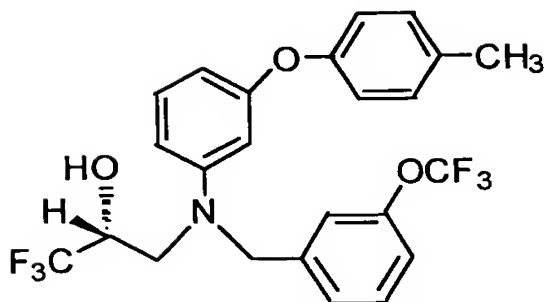
- 5 Additional examples (2*R*)-3-[[[(aryloxy)phenyl][[3-(trifluoromethoxy)phenyl] methyl]amino]-1,1,1-trifluoro-2-propanols can be prepared by one skilled in the art using similar methods, as shown in Example Table 6.

10 Example Table 6. (2*R*)-3-[[[(aryloxy)phenyl][[3-(trifluoromethoxy)phenyl] methyl]amino]-1,1,1-trifluoro-2-propanols.



<u>Ex.</u> <u>No.</u>	<u>R<sub>SUB</sub></u>	<u>Calculated</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>	<u>Observed</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>
34	3-trifluoromethoxy	556.1170	556.1180
35	3-isopropyl	514.1817	514.1823
36	3,4-dimethyl	500.1660	500.1654
37	4-chloro-3-methyl	520.1114	520.1129
38	3- <i>tert</i> -butyl	528.1973	528.1942
39	3,4-dichloro	540.0568	540.0567
40	3,4-(CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> )-	526.1817	526.1788

## EXAMPLE 41



5      **(2R)-3-[[3-(4-methylphenoxy)phenyl][[3-(trifluoromethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol**

**EX-41A)** To a solution of *p*-cresol (5.76 g, 0.053 mol) and 1,3-dinitrobenzene (8.97 g, 0.053 mol) in 100 mL of dimethylsulfoxide was added cesium carbonate (43.4 g, 0.133 mol). The reaction mixture was heated at 100 °C for 18 h, then cooled to room temperature, quenched with water, and extracted with diethyl ether. The organic layers were combined, washed with 0.1 N HCl and water, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 1:4 ethyl acetate in hexane to afford 8.0 g (66%) of the desired 3-(4-methylphenoxy)nitrobenzene product as a yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.83 (s, 1H), 7.64 (t, 1H), 7.32 (d, 1H), 7.18 (d, 1H), 7.09 (d, 2H), 6.8 (d, 2H), 2.20 (s, 1H).

**EX-41B)** A solution of 3-(4-methylphenoxy)nitrobenzene (8.0 g, 0.035 mol) from **EX-41A** in 25 mL of ethanol under nitrogen was charged with 10% palladium on carbon (0.80 g). The resulting mixture was hydrogenated for 4 h at room temperature and 45 psi. The reaction mixture was filtered through celite and concentrated *in vacuo* to give 6.7 g (96%) of the desired 3-(4-

methylphenoxy)aniline product as a yellow oil. ESMS  $m/z = 200$   $[M+H]^+$  confirmed the desired  $C_{13}H_{13}NO$  product and the complete consumption of starting material.

5

**EX-41C)** To a solution of 3-(4-methylphenoxy)aniline (2.91 g, 0.015 mol) from **EX-41B**, and 3-(trifluoromethoxy)benzaldehyde (3.24 g, 0.015 mol) in 50 mL dichloroethane was added sodium triacetoxyborohydride (4.02 g, 0.019 mol) and glacial acetic acid (0.99 g, 0.017 mol). The reaction mixture was stirred at room temperature for 18 h, then quenched with saturated aqueous sodium bicarbonate and extracted with dichloromethane. The organic layers were combined, dried over  $MgSO_4$  and concentrated *in vacuo* to give 5.38 g (91%) of the desired *N*-[3-(4-methylphenoxy)-phenyl]-[[3-(trifluoromethoxy)phenyl]methyl]amine product as an orange oil. ESMS  $m/z = 374$   $[M+H]^+$  confirmed the desired  $C_{21}H_{18}NO_2F_3$  product and the complete consumption of starting material.

15

To a mixture of *N*-[3-(4-methylphenoxy)phenyl]-[[3-(trifluoromethoxy)phenyl]methyl]amine (1.3 g, 0.0035 mol) from **EX-41C** and *R*-(+)-1,1,1-trifluoro-2,3-epoxypropane (0.59 g, 0.0053 mol) was added a suspension of ytterbium (III) trifluoromethanesulfonate (0.22 g, 0.0004 mol) in 1.3 mL of acetonitrile. The resulting mixture was heated at 50 °C in a sealed glass tube for 18 h. The reaction mixture was cooled to room temperature, then diluted with water and extracted with ethyl acetate. The crude product was purified by column chromatography on silica gel eluting with 1:4 ethyl acetate in hexane to afford 1.03 g (61%) of the desired (2*R*)-3-[3-(4-methylphenoxy)phenyl][[3-(trifluoromethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propa-nol product as a pure yellow oil. Anal. calcd. for  $C_{24}H_{21}F_6NO_3$ : C, 59.38; H, 4.36; N,

20

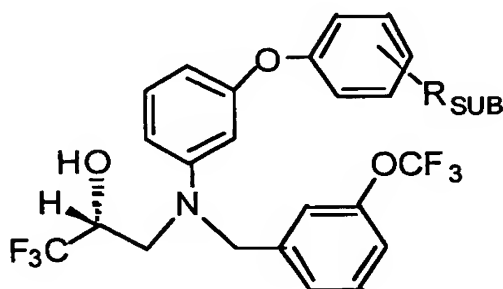
25

2.89. Found: C, 59.17; H, 4.62; N, 2.80. HRMS calcd.: 486.1504  $[M+H]^+$ ,  
 found: 486.1513.  $^1H$  NMR ( $C_6D_6$ )  $\delta$  6.82 (m, 8H), 6.60 (dd, 1H), 6.42 (dd,  
 1H), 6.38 (s, 1H), 6.18 (dd, 1H), 4.00 (s, 2H), 3.63 (m, 1H), 3.40 (d, 1H), 3.02  
 5 (m, 1H), 2.00 (s, 3H), 1.40 (d, 1H).  $^{19}F$  NMR ( $C_6D_6$ )  $\delta$  -57.98 (s, 3F), -78.50  
 (s, 3F).

Additional examples of (2*R*)-3-[3-(substituted-phenoxy)phenyl]-[[3-(trifluoro-methoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols can  
 10 prepared by one skilled in the art using similar methods, as shown in Example  
 Table 7.

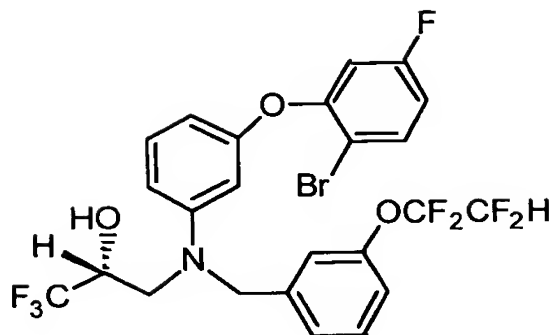
Example Table 7. (2*R*)- 3-[3-(substituted-phenoxy)phenyl][[3-(trifluoromethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols.

15



<u>Ex.</u> <u>No.</u>	<u>R<sub>SUB</sub></u>	<u>Calculated</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>	<u>Observed</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>
42	4-fluoro	490.1253	490.1238

## EXAMPLE 43



**(2R)-3-[[3-(2-bromo-5-fluorophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol**

**EX-43A)** To a solution of 3-aminophenol (5 g, 46 mmol), 1-bromo-2,4-difluorobenzene (10 g, 50 mmol) and  $\text{Cs}_2\text{CO}_3$  (16 g, 50 mmol) in 25 mL of dimethylformamide was added solid  $(\text{CuOTf})_2\text{C}_6\text{H}_6$  (100 mg), and the mixture was stirred under nitrogen at 85 °C for 22 h, at which time HPLC analysis indicated that the reaction had gone to completion and formed two products. The DMF was removed under reduced pressure. The residue was diluted with ether and filtered through a celite pad. The pad was washed with ether and a small amount of water. The mixture was extracted with ether several times. The combined ether layers were washed with water and brine, then dried over  $\text{MgSO}_4$ . The dried organic layer was evaporated to give 10.2 g (80%) of the desired product, which consisted of a 11:1 ratio of 3-(2-bromo-5-fluoro-phenoxy)aniline and 3-(4-bromo-3-fluorophenoxy)aniline. The crude product was purified by flash column chromatography on silica gel eluting with 1:7:0.01 of ethyl acetate:hexane:ammonium hydroxide to give 8.8 g (68%) of the desired product

as a yellow oil, which was a 25:1 ratio of 3-(2-bromo-5-fluorophenoxy)aniline and 3-(4-bromo-3-fluorophenoxy)aniline. HRMS calcd. for  $C_{12}H_9NOFBr$ : 281.9930  $[M+H]^+$ , found: 281.9950.

5

**EX-43B)** The 3-(2-bromo-5-fluorophenoxy)aniline (1.39 g, 4.95 mmol) product from **EX-43A** and 3-(1,1,2,2-tetrafluoroethoxy)benzaldehyde (1.0 g, 4.5 mmol) were dissolved in 15 mL of dichloroethane and acetic acid (0.30 mL, 5.4 mmol), then solid  $NaBH(OAc)_3$  (1.26 g, 5.9 mmol) was added. The mixture was stirred at room temperature for 1 h, then quenched with water and extracted with ether. The ether layer was washed with water and brine, then dried over  $MgSO_4$ , and evaporated to give 2.1 g (97%) of crude product, which was purified by flash column chromatography on silica gel eluting with 1:7:0.01 of ethyl acetate:hexane:ammonium hydroxide to give 2.0 g (91%) of the desired 3-[3-(2-bromo-5-fluoro-phenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amine product, as a light yellow oil, > 90% pure by HPLC analysis. HRMS calcd. for  $C_{21}H_{15}NO_2BrF_5$ : 488.0285  $[M+H]^+$ , found: 488.0269.

20 The 3-[3-(2-bromo-5-fluorophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amine (0.5 g, 2.0 mmol) product from **EX-43B** and *R*-(+)-1,1,1-trifluoro-2,3-epoxypropane (0.17 g, 2.0 mmol) from **EX-4** were dissolved in 0.5 mL of acetonitrile. Ytterbium (III) trifluoromethanesulfonate (0.06 g, 0.1 mmol) was added, and the stirred solution was warmed to 40 °C for 1 h, at which time HPLC analysis indicated that no secondary amine starting material remained. The reaction was quenched with water and extracted with ether. The ether layer

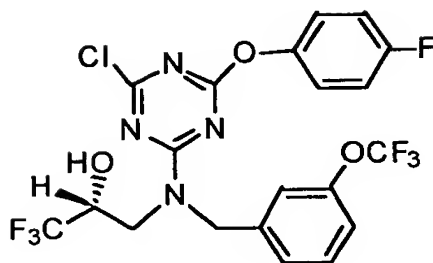
was washed with water and brine, then dried over  $\text{MgSO}_4$ . The crude product was purified by flash column chromatography on silica gel eluting with 1:7:0.01 of ethyl acetate:hexane:ammonium hydroxide to give 0.4 g (67%) of the desired

5 *R*-(+)-3-[[3-(2-bromo-5-fluorophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl] amino]-1,1,1-trifluoro-2-propanol product as a light yellow oil (> 84% ee by chiral HPLC analysis). Anal. calcd. for  $\text{C}_{24}\text{H}_{18}\text{BrF}_8\text{NO}_3$ : C, 48.02; H, 3.02; N, 2.33. found: C, 48.07; H, 3.14; N, 2.31. HRMS calcd.: 600.0420  $[\text{M}+\text{H}]^+$ , found: 600.0386.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.5 0 (dd, 1H), 7.30

10 (t, 1H), 7.18 (t, 1H), 7.07 (t, 2H), 6.99 (s, 1H), 6.70 (dt, 1H), 6.56 (dd, 1H), 6.52 (dd, 1H), 6.38 (dd, 1H), 6.32 (m, 1H), 5.87 (tt, 1H), 4.65 (d, 2H), 4.33 (m, 1H), 3.85 (dd, 1H), 3.56 (dd, 1H), 2.48 (bs, 1H). NOE difference spectra confirmed that the isolated material was the indicated *N*-[3-(2-bromo-5-fluoro-

15 phenoxy)phenyl]-3-aminopropanol product.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -79.24 (d, 3F), -88.57 (m, 2F), -112.04 (q, 1H), -137.16 (dt, 2F).

## EXAMPLE 44



5           **(2R)-N-[2-chloro-6-(p-fluorophenoxy)-1,3,5-triazin-4-yl]-3-[[[3-(trifluoromethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol**

**EX-44A)** 3-Trifluoromethoxybenzenemethanamine (1.15g, 6 mmol) and *R*-(+)-1,1,1-trifluoro-2,3-epoxypropane (0.67 g, 6 mmol) were combined and stirred at  
 10   80 °C for 1.5 h. The mixture was cooled to room temperature, and the resulting solid was recrystallized from hot hexanes. The white solid was isolated by vacuum filtration and washed with cold hexanes to give 0.67 g (37%) of pure (2R)-3-[[[3-(trifluoro-methoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.37 (t, 1H), 7.24 (d, 1H), 7.15 (m, 2H), 3.99  
 15   (m, 1H), 3.85 (d, 2H), 2.98 (dd, 1H), 2.88 (dd, 1H), 2.79 (s, 1H). <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ -58.19 (s, 3F), -78.88 (s, 3F). HRMS calcd. for C<sub>11</sub>H<sub>11</sub>F<sub>6</sub>NO<sub>2</sub>: 304.0772 [M+H]<sup>+</sup>, found: 304.0794.

**EX-44B)** To a solution of p-fluorophenol 1.00 g (8.92 mmol) in 30 mL of  
 20   tetrahydrofuran at 0 °C was added a 60% dispersion of sodium hydride in mineral oil (0.36 g, 8.92 mmol). After 30 min, cyanuric chloride (1.64 g, 8.92 mmol) was added as a heterogeneous mixture in tetrahydrofuran at 0 °C. The reaction mixture was allowed to slowly warm to room temperature. After 14 h,



the mixture was cooled to 0 °C, and a saturated aqueous NH<sub>4</sub>Cl solution was added. The aqueous solution was extracted with diethyl ether (3 x 50 mL). The combined ether extracts were washed with brine, dried (MgSO<sub>4</sub>), and concentrated *in vacuo* to afford 1.34 g (58%) of the desired 2,4-dichloro-6-(4-fluorophenoxy)-1,3,5-triazine product as an off white solid which was taken on to the next step without purification. MS *m/z* = 260 [M+H]<sup>+</sup>.

To a stirred solution of aminopropanol from EX-44A (0.100 g, 0.330 mmol) in *N,N*-dimethylformamide at 0 °C was added the 2,4-dichloro-(4-fluorophenoxy)-1,3,5-triazine ether product from EX-44B (0.086 g, 0.330 mmol) as a solution in *N,N*-di-methylformamide. The reaction mixture was allowed to slowly warm to room temperature. After 14 h, the reaction mixture was cooled to 0 °C, and a saturated aq. NaHCO<sub>3</sub> solution was added. After stirring the reaction mixture for 30 min at room temperature, the aqueous layer was extracted with ether (3 x 30 mL). The combined ether extracts were washed with brine, dried (MgSO<sub>4</sub>), and concentrated *in vacuo* to give a yellow oil. The crude residue was purified by column chromatography on silica gel eluting with 20 % ethyl acetate in hexanes to give 0.075 g (43%) of the desired (2*R*)-*N*-[2-chloro-6-(*p*-fluorophenoxy)-1,3,5-triazin-4-yl]-3-[[[3-(trifluoromethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as a pale yellow oil. HRMS calcd. for C<sub>20</sub>H<sub>14</sub>ClF<sub>7</sub>N<sub>4</sub>O<sub>3</sub>: 526.0643 [M<sup>+</sup>], found: 526.0632. <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>) δ 6.95 (s, 1H), 6.63 (m, 14H), 4.74 (d, 1H), 4.37 (d, 1H), 4.16 (d, 1H), 4.00 (d, 2H), 3.73 (m, 1H), 3.48 (m, 2H), 3.26 (m, 2H), 3.12 (m, 2H).

Based on the preceding procedures, additional substituted (2*R*)-3-[(*N*-aryl)-[[aryl]methyl]amino]-1,1,1-trifluoro-2-propanols are prepared by one

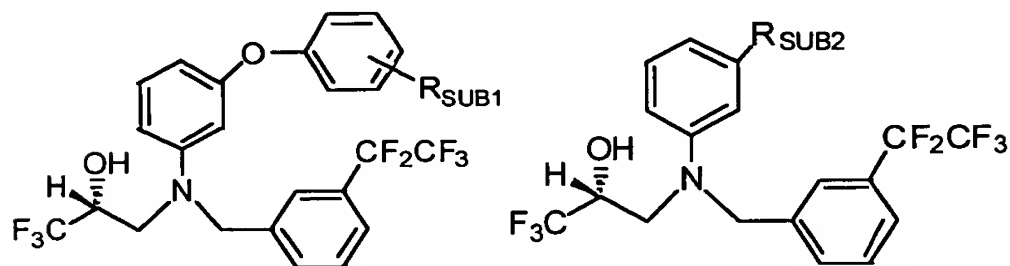
skilled in the art using similar methods, as shown in Example Table 8.

Substituted (3*R*)-4-[*N*-(aryl)-[(aryl)methyl]amino]-1,1,1,2,2-pentafluoro-3-butanols are prepared by one skilled in the art using similar methods, as shown in Example Table 9. Substituted (2*R*)-3-[*N*-(aryl)[(aryl)oxy]amino]-1,1,1-

- 5 trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Table 10. Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl]amino]-1,1-difluoro-1-chloro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Table 11.

- 10 Substituted (2*R*)-3-[*N,N'*-(diaryl)amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Table 12.

Example Table 8. Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl]amino]-1,1,1-trifluoro-2-propanols.



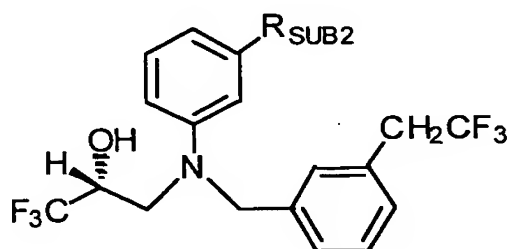
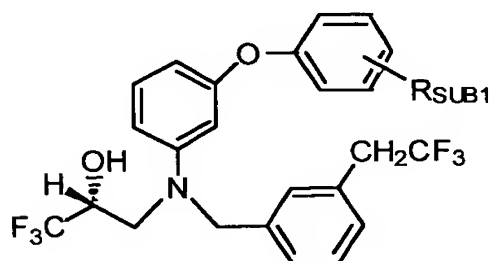
Ex. No.	R <sub>SUB1</sub>
45	3-isopropyl
46	2-Cl, 3-Cl
47	3-CF <sub>3</sub> O
48	4-F
49	4-CH <sub>3</sub>
50	2-F, 5-Br
51	3-CF <sub>3</sub> CF <sub>2</sub>
52	3-CH <sub>3</sub> CH <sub>2</sub>
53	3-CH <sub>3</sub> , 5-CH <sub>3</sub>
54	3-(CH <sub>3</sub> ) <sub>3</sub> C
55	4-F, 3-CH <sub>3</sub>
56	3-Cl, 4-Cl
57	3,4-(CH <sub>2</sub> ) <sub>4</sub>
58	3-HCF <sub>2</sub> CF <sub>2</sub> O
59	3-CHF <sub>2</sub> O
60	3-(CH <sub>3</sub> ) <sub>2</sub> N
61	3-cyclopropyl
62	3-(2-furyl)
63	3-CF <sub>3</sub> CF <sub>2</sub>
64	4-NH <sub>2</sub>
65	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>

Ex. No.	R <sub>SUB2</sub>
69	3-CF <sub>3</sub> O-benzyloxy
70	3-CF <sub>3</sub> -benzyloxy
71	3-F, 5-F-benzyloxy
72	cyclohexylmethyleneoxy
73	benzyloxy
74	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
75	4-CF <sub>3</sub> O-benzyloxy
76	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy
77	isopropoxy
78	3-CF <sub>3</sub> -benzyl
79	isopropylthio
80	cyclopentoxy
81	3-Cl-5-pyridinyloxy
82	3-CF <sub>3</sub> S-benzyloxy
83	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
84	2-F, 3-CF <sub>3</sub> -benzyloxy
85	3-F, 5-CF <sub>3</sub> -benzyloxy
86	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy
87	1-phenylethoxy
88	4-F, 3-CH <sub>3</sub> -benzoyl
89	3-CF <sub>3</sub> -phenyl

**Example Table 8 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl] amino]-1,1,1-trifluoro-2-propanols.**

<u>Ex.</u> <u>No.</u>	<u>R<sub>SUB1</sub></u>
66	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O
67	3-CF <sub>3</sub>
68	2-NO <sub>2</sub>

<u>Ex. No.</u>	<u>R<sub>SUB2</sub></u>
90	4-CH <sub>3</sub> O-phenylamino
91	cyclopropoxy
92	4-NO <sub>2</sub> -phenylthio



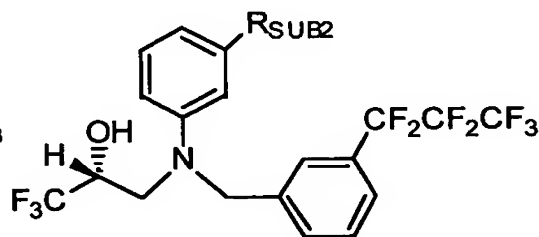
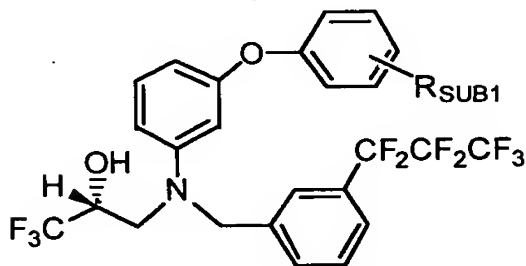
Ex. No.	<u>R<sub>SUB1</sub></u>
93	3-isopropyl
94	2-Cl, 3-Cl
95	3-CF <sub>3</sub> O
96	4-F
97	4-CH <sub>3</sub>
98	2-F, 5-Br
99	4-Cl, 3-CH <sub>3</sub> CH <sub>2</sub>
100	3-CH <sub>3</sub> CH <sub>2</sub>
101	3-CH <sub>3</sub> , 5-CH <sub>3</sub>
102	3-(CH <sub>3</sub> ) <sub>3</sub> C
103	4-F, 3-CH <sub>3</sub>
104	3-Cl, 4-Cl
105	3,4-(CH <sub>2</sub> ) <sub>4</sub>
106	3-HCF <sub>2</sub> CF <sub>2</sub> O
107	3-CHF <sub>2</sub> O

<u>Ex.</u> <u>No.</u>	<u>R<sub>SUB2</sub></u>
117	3-CF <sub>3</sub> O-benzyloxy
118	3-CF <sub>3</sub> -benzyloxy
119	3-F, 5-F-benzyloxy
120	cyclohexylmethyleneoxy
121	benzyloxy
122	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
123	4-CF <sub>3</sub> O-benzyloxy
124	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy
125	isopropoxy
126	3-CF <sub>3</sub> -benzyl
127	isopropylthio
128	cyclopentoxy
129	3-Cl-5-pyridinyloxy
130	3-CF <sub>3</sub> S-benzyloxy
131	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy

Example Table 8 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl] amino]-1,1,1-trifluoro-2-propanols.

Ex. No.	R <sub>SUB1</sub>
108	3-(CH <sub>3</sub> ) <sub>2</sub> N
109	3-cyclopropyl
110	3-(2-furyl)
111	3-CF <sub>3</sub> CF <sub>2</sub>
112	4-NH <sub>2</sub>
113	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>
114	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O
115	3-CF <sub>3</sub>
116	2-NO <sub>2</sub>

Ex. No.	R <sub>SUB2</sub>
132	2-F, 3-CF <sub>3</sub> -benzyloxy
133	3-F, 5-CF <sub>3</sub> -benzyloxy
134	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy
135	1-phenylethoxy
136	4-F, 3-CH <sub>3</sub> -benzoyl
137	3-CF <sub>3</sub> -phenyl
138	4-CH <sub>3</sub> O-phenylamino
139	cyclopropoxy
140	4-NO <sub>2</sub> -phenylthio



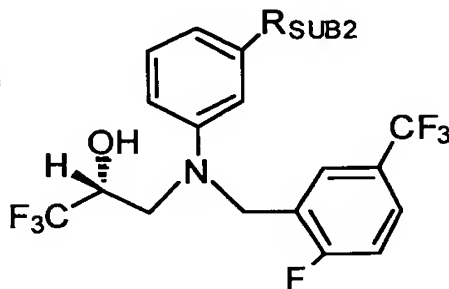
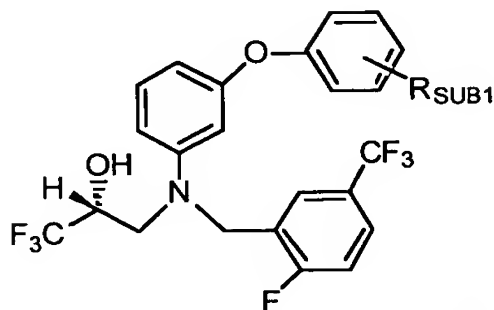
Ex. No.	R <sub>SUB1</sub>
141	3-isopropyl
142	2-Cl, 3-Cl
143	3-CF <sub>3</sub> O
144	4-F
145	4-CH <sub>3</sub>
146	2-F, 5-Br
147	4-Cl, 3-CH <sub>3</sub> CH <sub>2</sub>
148	3-CH <sub>3</sub> CH <sub>2</sub>

Ex. No.	R <sub>SUB2</sub>
165	3-CF <sub>3</sub> O-benzyloxy
166	3-CF <sub>3</sub> -benzyloxy
167	3-F, 5-F-benzyloxy
168	cyclohexylmethylenoxy
169	benzyloxy
170	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
171	4-CF <sub>3</sub> O-benzyloxy
172	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy

Example Table 8 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl] amino]-1,1,1-trifluoro-2-propanols.

<u>Ex. No.</u>	<u>R<sub>SUB1</sub></u>	<u>Ex. No.</u>	<u>R<sub>SUB2</sub></u>
149	3-CH <sub>3</sub> , 5-CH <sub>3</sub>	173	isopropoxy
150	3-(CH <sub>3</sub> ) <sub>3</sub> C	174	3-CF <sub>3</sub> -benzyl
151	4-F, 3-CH <sub>3</sub>	175	isopropylthio
152	3-Cl, 4-Cl	176	cyclopentoxy
153	3,4-(CH <sub>2</sub> ) <sub>4</sub>	177	3-Cl-5-pyridinyloxy
154	3-HCF <sub>2</sub> CF <sub>2</sub> O	178	3-CF <sub>3</sub> S-benzyloxy
155	3-CHF <sub>2</sub> O	179	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
156	3-(CH <sub>3</sub> ) <sub>2</sub> N	180	2-F, 3-CF <sub>3</sub> -benzyloxy
157	3-cyclopropyl	181	3-F, 5-CF <sub>3</sub> -benzyloxy
158	3-(2-furyl)	182	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy
159	3-CF <sub>3</sub> CF <sub>2</sub>	183	1-phenylethoxy
160	4-NH <sub>2</sub>	184	4-F, 3-CH <sub>3</sub> -benzoyl
161	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>	185	3-CF <sub>3</sub> -phenyl
162	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O	186	4-CH <sub>3</sub> O-phenylamino
163	3-CF <sub>3</sub>	187	cyclopropoxy
164	2-NO <sub>2</sub>	188	4-NO <sub>2</sub> -phenylthio

Example Table 8 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl] amino]-1,1,1-trifluoro-2-propanols.



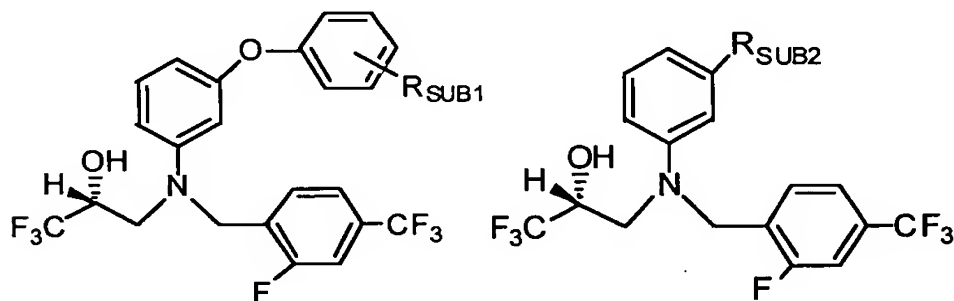
Ex. No.	$R_{SUB1}$
189	3-isopropyl
190	2-Cl, 3-Cl
191	3-CF <sub>3</sub> O
192	4-F
193	4-CH <sub>3</sub>
194	2-F, 5-Br
195	4-Cl, 3-CH <sub>3</sub>
196	3-CH <sub>3</sub> CH <sub>2</sub>
197	3-CH <sub>3</sub> , 5-CH <sub>3</sub>
198	3-(CH <sub>3</sub> ) <sub>3</sub> C
199	4-F, 3-CH <sub>3</sub>
200	3-Cl, 4-Cl
201	3,4-(CH <sub>2</sub> ) <sub>4</sub>
202	3-HCF <sub>2</sub> CF <sub>2</sub> O
203	3-CHF <sub>2</sub> O
204	3-(CH <sub>3</sub> ) <sub>2</sub> N
205	3-cyclopropyl
206	3-(2-furyl)
207	3-CF <sub>3</sub> CF <sub>2</sub>

Ex. No.	$R_{SUB2}$
213	3-CF <sub>3</sub> O-benzyloxy
214	3-CF <sub>3</sub> -benzyloxy
215	3-F, 5-F-benzyloxy
216	cyclohexylmethylenoxy
217	benzyloxy
218	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
219	4-CF <sub>3</sub> O-benzyloxy
220	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy
221	isopropoxy
222	3-CF <sub>3</sub> -benzyl
223	isopropylthio
224	cyclopentoxy
225	3-Cl-5-pyridinyloxy
226	3-CF <sub>3</sub> S-benzyloxy
227	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
228	2-F, 3-CF <sub>3</sub> -benzyloxy
229	3-F, 5-CF <sub>3</sub> -benzyloxy
230	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy
231	1-phenylethoxy

Example Table 8 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl] amino]-1,1,1-trifluoro-2-propanols.

<u>Ex. No.</u>	<u>R<sub>SUB1</sub></u>
208	4-NH <sub>2</sub>
209	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>
210	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O
211	3-CF <sub>3</sub>
212	2-NO <sub>2</sub>

<u>Ex. No.</u>	<u>R<sub>SUB2</sub></u>
232	4-F, 3-CH <sub>3</sub> -benzoyl
233	3-CF <sub>3</sub> -phenyl
234	4-CH <sub>3</sub> O-phenylamino
235	cyclopropoxy
236	4-NO <sub>2</sub> -phenylthio



<u>Ex. No.</u>	<u>R<sub>SUB1</sub></u>
237	3-isopropyl
238	2-Cl, 3-Cl
239	3-CF <sub>3</sub> O
240	4-F
241	4-CH <sub>3</sub>
242	2-F, 5-Br
243	4-Cl, 3-CH <sub>3</sub>
244	3-CH <sub>3</sub> CH <sub>2</sub>
245	3-CH <sub>3</sub> , 5-CH <sub>3</sub>
246	3-(CH <sub>3</sub> ) <sub>3</sub> C
247	4-F, 3-CH <sub>3</sub>
248	3-Cl, 4-Cl

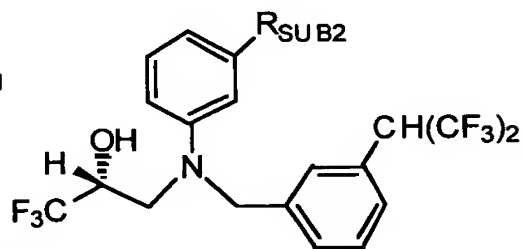
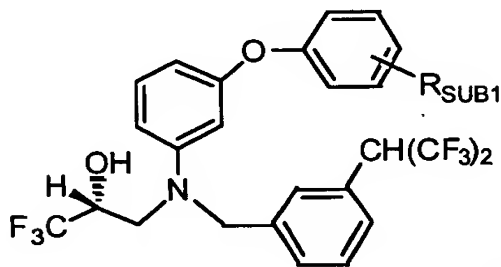
<u>Ex. No.</u>	<u>R<sub>SUB2</sub></u>
261	3-CF <sub>3</sub> O-benzyloxy
262	3-CF <sub>3</sub> -benzyloxy
263	3-F, 5-F-benzyloxy
264	cyclohexylmethyleneoxy
265	benzyloxy
266	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
267	4-CF <sub>3</sub> O-benzyloxy
268	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy
269	isopropoxy
270	3-CF <sub>3</sub> -benzyl
271	isopropylthio
272	cyclopentoxy



Example Table 8 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl] amino]-1,1,1-trifluoro-2-propanols.

Ex. No.	R <sub>SUB1</sub>
249	3,4-(CH <sub>2</sub> ) <sub>4</sub>
250	3-HCF <sub>2</sub> CF <sub>2</sub> O
251	3-CHF <sub>2</sub> O
252	3-(CH <sub>3</sub> ) <sub>2</sub> N
253	3-cyclopropyl
254	3-(2-furyl)
255	3-CF <sub>3</sub> CF <sub>2</sub>
256	4-NH <sub>2</sub>
257	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>
258	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O
259	3-CF <sub>3</sub>
260	2-NO <sub>2</sub>

Ex. No.	R <sub>SUB2</sub>
273	3-Cl-5-pyridinyloxy
274	3-CF <sub>3</sub> S-benzyloxy
275	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
276	2-F, 3-CF <sub>3</sub> -benzyloxy
277	3-F, 5-CF <sub>3</sub> -benzyloxy
278	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy
279	1-phenylethoxy
280	4-F, 3-CH <sub>3</sub> -benzoyl
281	3-CF <sub>3</sub> -phenyl
282	4-CH <sub>3</sub> O-phenylamino
283	cyclopropoxy
284	4-NO <sub>2</sub> -phenylthio



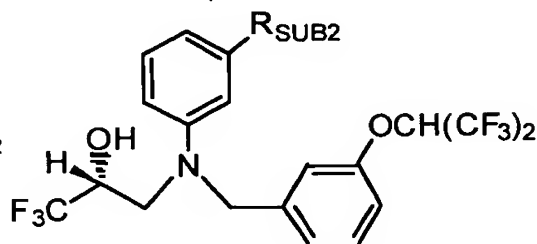
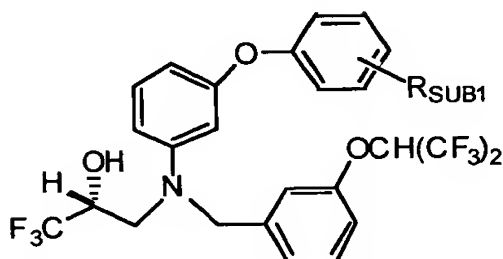
Ex. No.	R <sub>SUB1</sub>
285	3-isopropyl
286	2-Cl, 3-Cl
287	3-CF <sub>3</sub> O
288	4-F
289	4-CH <sub>3</sub>

Ex. No.	R <sub>SUB2</sub>
309	3-CF <sub>3</sub> O-benzyloxy
310	3-CF <sub>3</sub> -benzyloxy
311	3-F, 5-F-benzyloxy
312	cyclohexylmethylenedioxy
313	benzyloxy

Example Table 8 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl] amino]-1,1,1-trifluoro-2-propanols.

<u>Ex. No.</u>	<u>R<sub>SUB1</sub></u>	<u>Ex. No.</u>	<u>R<sub>SUB2</sub></u>
290	2-F, 5-Br	314	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
291	4-Cl, 3-CH <sub>3</sub> CH <sub>2</sub>	315	4-CF <sub>3</sub> O-benzyloxy
292	3-CH <sub>3</sub> CH <sub>2</sub>	316	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy
293	3-CH <sub>3</sub> , 5-CH <sub>3</sub>	317	isopropoxy
294	3-(CH <sub>3</sub> ) <sub>3</sub> C	318	3-CF <sub>3</sub> -benzyl
295	4-F, 3-CH <sub>3</sub>	319	isopropylthio
296	3-Cl, 4-Cl	320	cyclopentoxy
297	3,4-(CH <sub>2</sub> ) <sub>4</sub>	321	3-Cl-5-pyridinyloxy
298	3-HCF <sub>2</sub> CF <sub>2</sub> O	322	3-CF <sub>3</sub> S-benzyloxy
299	3-CHF <sub>2</sub> O	323	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
300	3-(CH <sub>3</sub> ) <sub>2</sub> N	324	2-F, 3-CF <sub>3</sub> -benzyloxy
301	3-cyclopropyl	325	3-F, 5-CF <sub>3</sub> -benzyloxy
302	3-(2-furyl)	326	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy
303	3-CF <sub>3</sub> CF <sub>2</sub>	327	1-phenylethoxy
304	4-NH <sub>2</sub>	328	4-F, 3-CH <sub>3</sub> -benzoyl
305	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>	329	3-CF <sub>3</sub> -phenyl
306	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O	330	4-CH <sub>3</sub> O-phenylamino
307	3-CF <sub>3</sub>	331	cyclopropoxy
308	2-NO <sub>2</sub>	332	4-NO <sub>2</sub> -phenylthio

Example Table 8 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl] amino]-1,1,1-trifluoro-2-propanols.



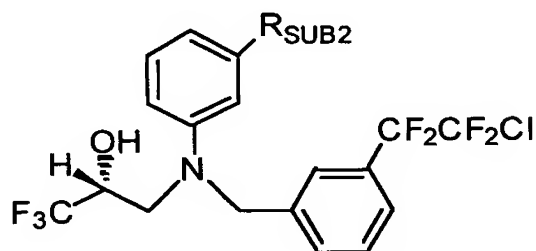
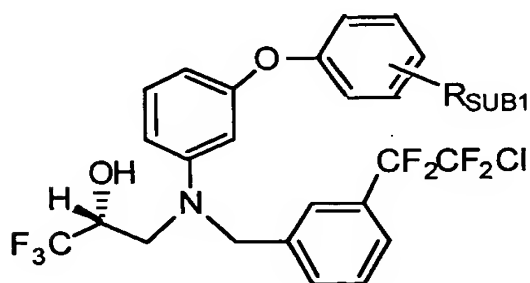
Ex. No.	R <sub>SUB1</sub>
333	3-isopropyl
334	2-Cl, 3-Cl
335	3-CF <sub>3</sub> O
336	4-F
337	4-CH <sub>3</sub>
338	2-F, 5-Br
339	4-Cl, 3-CH <sub>3</sub> CH <sub>2</sub>
340	3-CH <sub>3</sub> CH <sub>2</sub>
341	3-CH <sub>3</sub> , 5-CH <sub>3</sub>
342	3-(CH <sub>3</sub> ) <sub>3</sub> C
343	4-F, 3-CH <sub>3</sub>
344	3-Cl, 4-Cl
345	3,4-(CH <sub>2</sub> ) <sub>4</sub>
346	3-HCF <sub>2</sub> CF <sub>2</sub> O
347	3-CHF <sub>2</sub> O
348	3-(CH <sub>3</sub> ) <sub>2</sub> N
349	3-cyclopropyl
350	3-(2-furyl)
351	3-CF <sub>3</sub> CF <sub>2</sub>
352	4-NH <sub>2</sub>

Ex. No.	R <sub>SUB2</sub>
357	3-CF <sub>3</sub> O-benzyloxy
358	3-CF <sub>3</sub> -benzyloxy
359	3-F, 5-F-benzyloxy
360	cyclohexylmethylenedioxy
361	benzyloxy
362	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
363	4-CF <sub>3</sub> O-benzyloxy
364	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy
365	isopropoxy
366	3-CF <sub>3</sub> -benzyl
367	isopropylthio
368	cyclopentoxo
369	3-Cl-5-pyridinyloxy
370	3-CF <sub>3</sub> S-benzyloxy
371	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
372	2-F, 3-CF <sub>3</sub> -benzyloxy
373	3-F, 5-CF <sub>3</sub> -benzyloxy
374	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy
375	1-phenylethoxy
376	4-F, 3-CH <sub>3</sub> -benzoyl

Example Table 8 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl] amino]-1,1,1-trifluoro-2-propanols.

<u>Ex. No.</u>	<u>R<sub>SUB1</sub></u>
353	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>
354	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O
355	3-CF <sub>3</sub>
356	2-NO <sub>2</sub>

<u>Ex. No.</u>	<u>R<sub>SUB2</sub></u>
377	3-CF <sub>3</sub> -phenyl
378	4-CH <sub>3</sub> O-phenylamino
379	cyclopropoxy
380	4-NO <sub>2</sub> -phenylthio

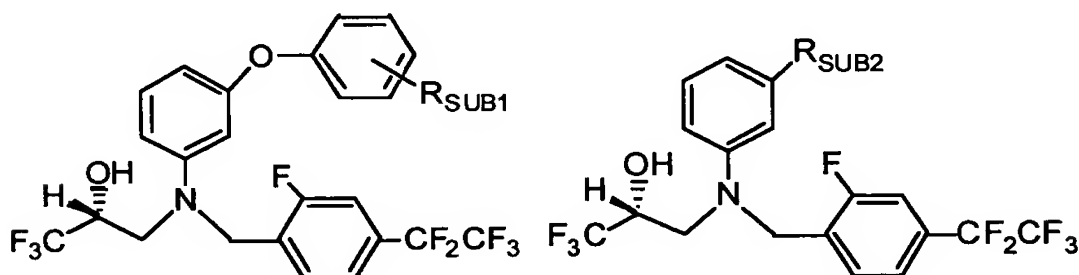


<u>Ex. No.</u>	<u>R<sub>SUB1</sub></u>
381	3-isopropyl
382	2-Cl, 3-Cl
383	3-CF <sub>3</sub> O
384	4-F
385	4-CH <sub>3</sub>
386	2-F, 5-Br
387	4-Cl, 3-CH <sub>3</sub> CH <sub>2</sub>
388	3-CH <sub>3</sub> CH <sub>2</sub>
389	3-CH <sub>3</sub> , 5-CH <sub>3</sub>
390	3-(CH <sub>3</sub> ) <sub>3</sub> C
391	4-F, 3-CH <sub>3</sub>
392	3-Cl, 4-Cl
393	3,4-(CH <sub>2</sub> ) <sub>4</sub>

<u>Ex. No.</u>	<u>R<sub>SUB2</sub></u>
405	3-CF <sub>3</sub> O-benzyloxy
406	3-CF <sub>3</sub> -benzyloxy
407	3-F, 5-F-benzyloxy
408	cyclohexylmethylenoxy
409	benzyloxy
410	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
411	4-CF <sub>3</sub> O-benzyloxy
412	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy
413	isopropoxy
414	3-CF <sub>3</sub> -benzyl
415	isopropylthio
416	cyclopentoxy
417	3-Cl-5-pyridinyloxy

Example Table 8 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl] amino]-1,1,1-trifluoro-2-propanols.

Ex. No.	R <sub>SUB1</sub>	Ex. No.	R <sub>SUB2</sub>
394	3-HCF <sub>2</sub> CF <sub>2</sub> O	418	3-CF <sub>3</sub> S-benzyloxy
395	3-CHF <sub>2</sub> O	419	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
396	3-(CH <sub>3</sub> ) <sub>2</sub> N	420	2-F, 3-CF <sub>3</sub> -benzyloxy
397	3-cyclopropyl	421	3-F, 5-CF <sub>3</sub> -benzyloxy
398	3-(2-furyl)	422	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy
399	3-CF <sub>3</sub> CF <sub>2</sub>	423	1-phenylethoxy
400	4-NH <sub>2</sub>	424	4-F, 3-CH <sub>3</sub> -benzoyl
401	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>	425	3-CF <sub>3</sub> -phenyl
402	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O	426	4-CH <sub>3</sub> O-phenylamino
403	3-CF <sub>3</sub>	427	cyclopropoxy
404	2-NO <sub>2</sub>	428	4-NO <sub>2</sub> -phenylthio

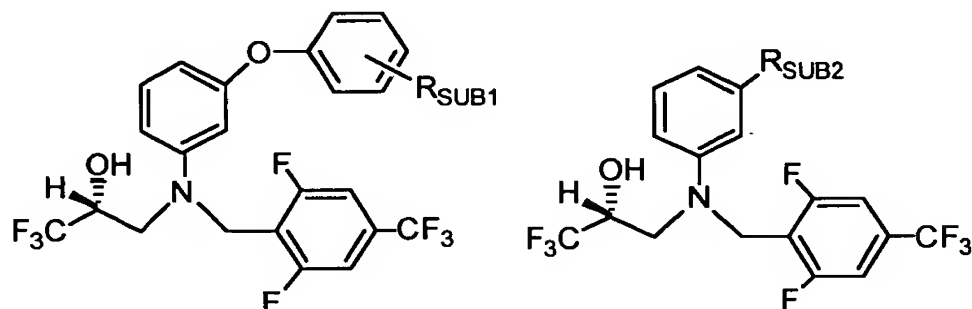


Ex. No.	R <sub>SUB1</sub>	Ex. No.	R <sub>SUB2</sub>
429	3-isopropyl	453	3-CF <sub>3</sub> O-benzyloxy
430	2-Cl, 3-Cl	454	3-CF <sub>3</sub> -benzyloxy
431	3-CF <sub>3</sub> O	455	3-F, 5-F-benzyloxy
432	4-F	456	cyclohexylmethyleneoxy
433	4-CH <sub>3</sub>	457	benzyloxy
434	2-F, 5-Br	458	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy

Example Table 8 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl] amino]-1,1,1-trifluoro-2-propanols.

<u>Ex. No.</u>	<u>R<sub>SUB1</sub></u>	<u>Ex. No.</u>	<u>R<sub>SUB2</sub></u>
435	4-Cl, 3-CH <sub>3</sub> CH <sub>2</sub>	459	4-CF <sub>3</sub> O-benzyloxy
436	3-CH <sub>3</sub> CH <sub>2</sub>	460	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy
437	3-CH <sub>3</sub> , 5-CH <sub>3</sub>	461	isopropoxy
438	3-(CH <sub>3</sub> ) <sub>3</sub> C	462	3-CF <sub>3</sub> -benzyl
439	4-F, 3-CH <sub>3</sub>	463	isopropylthio
440	3-Cl, 4-Cl	464	cyclopentoxy
441	3,4-(CH <sub>2</sub> ) <sub>4</sub>	465	3-Cl-5-pyridinyloxy
442	3-HCF <sub>2</sub> CF <sub>2</sub> O	466	3-CF <sub>3</sub> S-benzyloxy
443	3-CHF <sub>2</sub> O	467	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
444	3-(CH <sub>3</sub> ) <sub>2</sub> N	468	2-F, 3-CF <sub>3</sub> -benzyloxy
445	3-cyclopropyl	469	3-F, 5-CF <sub>3</sub> -benzyloxy
446	3-(2-furyl)	470	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy
447	3-CF <sub>3</sub> CF <sub>2</sub>	471	1-phenylethoxy
448	4-NH <sub>2</sub>	472	4-F, 3-CH <sub>3</sub> -benzoyl
449	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>	473	3-CF <sub>3</sub> -phenyl
450	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O	474	4-CH <sub>3</sub> O-phenylamino
451	3-CF <sub>3</sub>	475	cyclopropoxy
452	2-NO <sub>2</sub>	476	4-NO <sub>2</sub> -phenylthio

Example Table 8 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl] amino]-1,1,1-trifluoro-2-propanols.



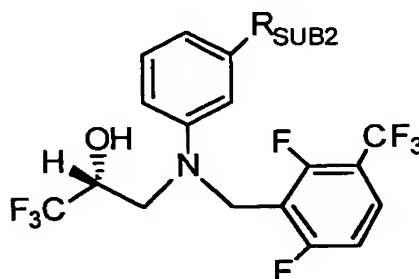
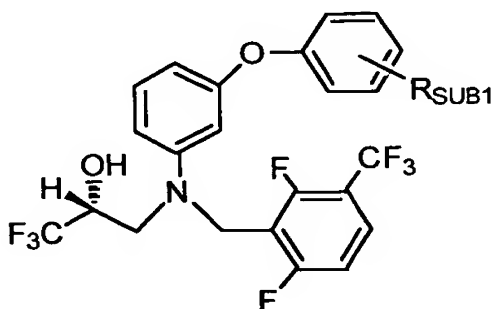
Ex. No.	R <sub>SUB1</sub>
477	3-isopropyl
478	2-Cl, 3-Cl
479	3-CF <sub>3</sub> O
480	4-F
481	4-CH <sub>3</sub>
482	2-F, 5-Br
483	4-Cl, 3-CH <sub>3</sub> CH <sub>2</sub>
484	3-CH <sub>3</sub> CH <sub>2</sub>
485	3-CH <sub>3</sub> , 5-CH <sub>3</sub>
486	3-(CH <sub>3</sub> ) <sub>3</sub> C
487	4-F, 3-CH <sub>3</sub>
488	3-Cl, 4-Cl
489	3,4-(CH <sub>2</sub> ) <sub>4</sub>
490	3-HCF <sub>2</sub> CF <sub>2</sub> O
491	3-CHF <sub>2</sub> O
492	3-(CH <sub>3</sub> ) <sub>2</sub> N
493	3-cyclopropyl
494	3-(2-furyl)
495	3-CF <sub>3</sub> CF <sub>2</sub>

Ex. No.	R <sub>SUB2</sub>
501	3-CF <sub>3</sub> O-benzyloxy
502	3-CF <sub>3</sub> -benzyloxy
503	3-F, 5-F-benzyloxy
504	cyclohexylmethylenoxy
505	benzyloxy
506	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
507	4-CF <sub>3</sub> O-benzyloxy
508	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy
509	isopropoxy
510	3-CF <sub>3</sub> -benzyl
511	isopropylthio
512	cyclopentoxy
513	3-Cl-5-pyridinyloxy
514	3-CF <sub>3</sub> S-benzyloxy
515	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
516	2-F, 3-CF <sub>3</sub> -benzyloxy
517	3-F, 5-CF <sub>3</sub> -benzyloxy
518	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy
519	1-phenylethoxy

Example Table 8 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl] amino]-1,1,1-trifluoro-2-propanols.

Ex. No.	R <sub>SUB1</sub>
496	4-NH <sub>2</sub>
497	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>
498	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O
499	3-CF <sub>3</sub>
500	2-NO <sub>2</sub>

Ex. No.	R <sub>SUB2</sub>
520	4-F, 3-CH <sub>3</sub> -benzoyl
521	3-CF <sub>3</sub> -phenyl
522	4-CH <sub>3</sub> O-phenylamino
523	cyclopropoxy
524	4-NO <sub>2</sub> -phenylthio



Ex. No.	R <sub>SUB1</sub>
525	3-isopropyl
526	2-Cl, 3-Cl
527	3-CF <sub>3</sub> O
528	4-F
529	4-CH <sub>3</sub>
530	2-F, 5-Br
531	4-Cl, 3-CH <sub>3</sub> CH <sub>2</sub>
532	3-CH <sub>3</sub> CH <sub>2</sub>
533	3-CH <sub>3</sub> , 5-CH <sub>3</sub>
534	3-(CH <sub>3</sub> ) <sub>3</sub> C
535	4-F, 3-CH <sub>3</sub>
536	3-Cl, 4-Cl

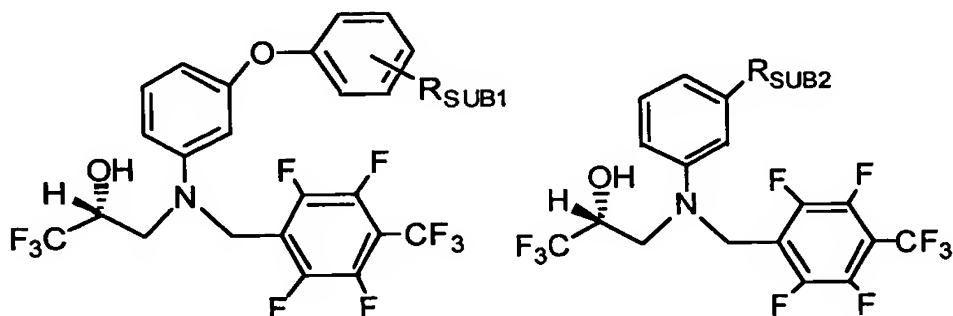
Ex. No.	R <sub>SUB2</sub>
549	3-CF <sub>3</sub> O-benzyloxy
550	3-CF <sub>3</sub> -benzyloxy
551	3-F, 5-F-benzyloxy
552	cyclohexylmethylenedioxy
553	benzyloxy
554	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
555	4-CF <sub>3</sub> O-benzyloxy
556	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy
557	isopropoxy
558	3-CF <sub>3</sub> -benzyl
559	isopropylthio
560	cyclopentoxy



Example Table 8 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl] amino]-1,1,1-trifluoro-2-propanols.

<u>Ex. No.</u>	<u>R<sub>SUB1</sub></u>
537	3,4-(CH <sub>2</sub> ) <sub>4</sub>
538	3-HCF <sub>2</sub> CF <sub>2</sub> O
539	3-CHF <sub>2</sub> O
540	3-(CH <sub>3</sub> ) <sub>2</sub> N
541	3-cyclopropyl
542	3-(2-furyl)
543	3-CF <sub>3</sub> CF <sub>2</sub>
544	4-NH <sub>2</sub>
545	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>
546	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O
547	3-CF <sub>3</sub>
548	2-NO <sub>2</sub>

<u>Ex. No.</u>	<u>R<sub>SUB2</sub></u>
561	3-Cl-5-pyridinyloxy
562	3-CF <sub>3</sub> S-benzyloxy
563	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
564	2-F, 3-CF <sub>3</sub> -benzyloxy
565	3-F, 5-CF <sub>3</sub> -benzyloxy
566	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy
567	1-phenylethoxy
568	4-F, 3-CH <sub>3</sub> -benzoyl
569	3-CF <sub>3</sub> -phenyl
570	4-CH <sub>3</sub> O-phenylamino
571	cyclopropoxy
572	4-NO <sub>2</sub> -phenylthio



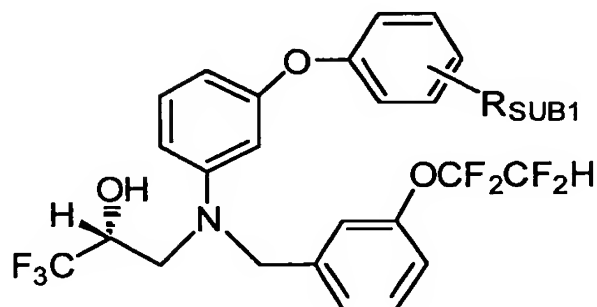
<u>Ex. No.</u>	<u>R<sub>SUB1</sub></u>
573	3-isopropyl
574	2-Cl, 3-Cl
575	3-CF <sub>3</sub> O
576	4-F

<u>Ex. No.</u>	<u>R<sub>SUB2</sub></u>
597	3-CF <sub>3</sub> O-benzyloxy
598	3-CF <sub>3</sub> -benzyloxy
599	3-F, 5-F-benzyloxy
600	cyclohexylmethyleneoxy

Example Table 8 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl] amino]-1,1,1-trifluoro-2-propanols.

<u>Ex. No.</u>	<u>R<sub>SUB1</sub></u>	<u>Ex. No.</u>	<u>R<sub>SUB2</sub></u>
577	4-CH <sub>3</sub>	601	benzyloxy
578	2-F, 5-Br	602	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
579	4-Cl, 3-CH <sub>3</sub> CH <sub>2</sub>	603	4-CF <sub>3</sub> O-benzyloxy
580	3-CH <sub>3</sub> CH <sub>2</sub>	604	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy
581	3-CH <sub>3</sub> , 5-CH <sub>3</sub>	605	isopropoxy
582	3-(CH <sub>3</sub> ) <sub>3</sub> C	606	3-CF <sub>3</sub> -benzyl
583	4-F, 3-CH <sub>3</sub>	607	isopropylthio
584	3-Cl, 4-Cl	608	cyclopentoxy
585	3,4-(CH <sub>2</sub> ) <sub>4</sub>	609	3-Cl-5-pyridinyloxy
586	3-HCF <sub>2</sub> CF <sub>2</sub> O	610	3-CF <sub>3</sub> S-benzyloxy
587	3-CHF <sub>2</sub> O	611	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
588	3-(CH <sub>3</sub> ) <sub>2</sub> N	612	2-F, 3-CF <sub>3</sub> -benzyloxy
589	3-cyclopropyl	613	3-F, 5-CF <sub>3</sub> -benzyloxy
590	3-(2-furyl)	614	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy
591	3-CF <sub>3</sub> CF <sub>2</sub>	615	1-phenylethoxy
592	4-NH <sub>2</sub>	616	4-F, 3-CH <sub>3</sub> -benzoyl
593	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>	617	3-CF <sub>3</sub> -phenyl
594	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O	618	4-CH <sub>3</sub> O-phenylamino
595	3-CF <sub>3</sub>	619	cyclopropoxy
596	2-NO <sub>2</sub>	620	4-NO <sub>2</sub> -phenylthio

Example Table 8 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl] amino]-1,1,1-trifluoro-2-propanols.



<u>Ex.</u> <u>No.</u>	<u>R<sub>SUB1</sub></u>	<u>Calculated</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>	<u>Observed</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>
621	4-F	522.1315	522.1297
622	2-Cl, 3-Cl	572.0630	572.0653
623	2-F, 5-Br	600.0420	600.0404
624	4-Cl, 3-CH <sub>3</sub>	551.1098	551.1101
625	3-CH <sub>3</sub> , 5-CH <sub>3</sub>	532.1722	532.1705
626	3-(CH <sub>3</sub> ) <sub>3</sub> C	560.2035	560.2055
627	4-F, 3-CH <sub>3</sub>	536.1471	536.1480
628	3-Cl, 4-Cl	572.0630	572.0630
629	3,4-(CH <sub>2</sub> ) <sub>4</sub>	558.1879	558.1881
630	3-HCF <sub>2</sub> CF <sub>2</sub> O		
631	3-CHF <sub>2</sub> O		
632	3-(CH <sub>3</sub> ) <sub>2</sub> N	547.1831	547.1844
633	3-cyclopropyl		
634	3-(2-furyl)		
635	3-CF <sub>3</sub> CF <sub>2</sub>		
636	3-cyclopentyl		
637	4-NH <sub>2</sub>	519.1519	519.1529

Example Table 8 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl] amino]-1,1,1-trifluoro-2-propanols.

<u>Ex.</u> <u>No.</u>	<u>R<sub>SUB1</sub></u>	<u>Calculated</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>	<u>Observed</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>
638	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>	546.1879	546.1901
639	4-CH <sub>3</sub> CH <sub>2</sub> O	547.1594	547.1594
640	3-CF <sub>3</sub>		
641	2-NO <sub>2</sub>	549.1260	549.1235
642	3,4-dimethyl	531.1644	531.1649
643	3-methyl, 5-ethyl	546.1879	546.1899
644	3-methyl	517.1488	517.1493
645	2,3-difluoro	540.1221	540.1182
646	4-CF <sub>3</sub>	572.1282	572.1268
647	2-fluoro, 3-CF <sub>3</sub>	590.1189	590.1184
648	2-fluoro, 4-CF <sub>3</sub>	590.1189	590.1155
649	2-chloro, 4-fluoro	556.0925	556.0891
650	4- <i>n</i> -propyl	546.1879	546.1878
651	3-chloro, 4-fluoro	556.0925	556.0932
652	2,4-difluoro	540.1221	540.1194
653	3,5-difluoro	540.1221	540.1217
654	3,4-difluoro	540.1221	540.1248
655	3-fluoro	522.1315	522.1337
656	2-chloro	538.1019	538.1021
657	2-fluoro	522.1315	522.1310
658	2,5-difluoro	540.1221	540.1255
659	4-chloro, 2-fluoro	556.0926	556.0954
660	2,4-dichloro	572.0630	572.0667
661	2-fluoro, 3-CH <sub>3</sub>		
662	4-chloro	537.0942	537.0944

Example Table 8 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl] amino]-1,1,1-trifluoro-2-propanols.

<u>Ex.</u> <u>No.</u>	<u>R<sub>SUB1</sub></u>	<u>Calculated</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>	<u>Observed</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>
663	4-isopropyl, 3-methyl	560.2035	560.2035
664	2,3,4-trifluoro	558.1127	558.1161
665	2,3,5-trifluoro	558.1127	558.1109
666	4-propoxy	562.1828	562.1803
667	4-isopropyl	546.1879	546.1899
668	4-CF <sub>3</sub> O-	588.1233	588.1241
669	4-butoxy	576.1958	576.1969
670	3-methyl, 4-CH <sub>3</sub> S-	564.1443	564.1476
671	4-nitro	549.1260	549.1306
672	3-CF <sub>3</sub> S-		
673	4-chloro, 3-fluoro	556.0925	556.0933
674	3,5-dimethoxy	564.1623	564.1617
675	4-bromo	582.0716	582.0473
676	4- <i>sec</i> -butyl	560.2035	560.2051
677	3-fluoro-2-nitro	567.1166	567.1135
678	3-methoxy	533.1437	533.1450
679	4-bromo-2-nitro	627.0366	627.0375
680	4-cyano	529.1362	529.1364
681	4-CH <sub>3</sub> S-	550.1209	550.1251
682	3,4-(CH=CH) <sub>2</sub>	554.1566	554.1578
683	4-CH <sub>3</sub> CH <sub>2</sub> NH-	547.1832	547.1819
684	4-propionyl	560.1672	560.1694
685	3-phenyl	580.1723	580.1772
686	4-cyclopentyl	572.2035	572.2029

FC(F)(F)C(O)CN(Cc1ccc(OC(F)F)cc1)c2ccc(RSUB2)cc2

<u>Ex.</u> <u>No.</u>	<u>R<sub>SUB2</sub></u>	<u>Calculated</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>	<u>Observed</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>
687	6-methyl-3-pyridinyloxy	518.1440	518.1452
688	5-chloro-3-pyridinyloxy	539.0972	539.1002
689	3-pyridinyloxy	505.1362	505.1369
690	2-methyl-3-pyridinyloxy	519.1518	519.1517
691	5-indolinyloxy	543.1519	543.1630
692	4-fluoro-2-pyridinyloxy	523.1268	523.1243
693	2-cyano-3-pyridinyloxy	530.1315	530.1300
694	5-bromo-2-pyridinyloxy	583.0667	583.0405
695	3-CF <sub>3</sub> -2-pyridinyloxy	573.1236	573.1205
696	2-pyridinylmethylenoxy	519.1519	519.1522
697	cyclohexylmethylenoxy	524.2036	524.2028
698	isopropoxy	470.1488	470.1565
699	cyclopentyloxy	496.1723	496.1719
700	neo-pentoxy	498.1879	498.1845
701	4-(methoxycarbonyl)-butoxy	542.1777	542.1827
702	trifluoromethoxy	496.0971	496.0959
703	2-methylpropoxy	484.1723	484.1718
704	2-methoxyethoxy	486.1515	486.1537
705	2-oxobutoxy	498.1515	498.1529
706	cyclohexyloxy	510.1880	510.1910

Example Table 8 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl] amino]-1,1,1-trifluoro-2-propanols.

<u>Ex.</u> <u>No.</u>	<u>R<sub>SUB2</sub></u>	<u>Calculated</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>	<u>Observed</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>
707	(methoxycarbonyl)methoxy	500.1308	500.1297
708	4-tetrahydropyranyloxy	512.1672	512.1631
709	1-phenylethoxy	532.1723	532.1711
710	3-CF <sub>3</sub> O-benzyloxy	602.1389	602.1380
711	3-trifluoromethyl-benzyloxy	586.1440	586.1419
712	3,5-dimethyl-benzyloxy	546.1879	546.1890
713	3-bromo-benzyloxy	596.0671	596.0641
714	3-CF <sub>3</sub> S-benzyloxy	618.1161	618.1151
715	3,4-dimethyl-benzyloxy	546.1879	546.1881
716	3,5-difluoro-benzyloxy	554.1378	554.1390
717	2-fluoro-3-CF <sub>3</sub> -benzyloxy	604.1346	604.1329
718	benzyloxy	518.1566	518.1578
719	3,5-(CF <sub>3</sub> ) <sub>2</sub> -benzyloxy	654.1314	654.1308
720	3-fluoro-5-CF <sub>3</sub> -benzyloxy	604.1346	604.1309
721	4-CF <sub>3</sub> O-benzyloxy	602.1389	602.1383
722	3-chloro-benzyloxy	552.1176	552.1157
723	4-ethyl-benzyloxy	546.1879	546.1862
724	3-methyl-benzyloxy	532.1723	532.1692
725	2-fluoro-benzyloxy	536.1472	536.1465
726	2,3-difluoro-benzyloxy	554.1378	554.1364
727	4-isopropyl-benzyloxy	560.2036	560.2020
728	4-methyl-benzyloxy	532.1723	532.1729
729	4-bromo-benzyloxy	596.0671	596.0669
730	4-CF <sub>3</sub> -benzyloxy	586.1440	586.1400
731	4-fluoro-benzyloxy	536.1472	536.1454

Example Table 8 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl] amino]-1,1,1-trifluoro-2-propanols.

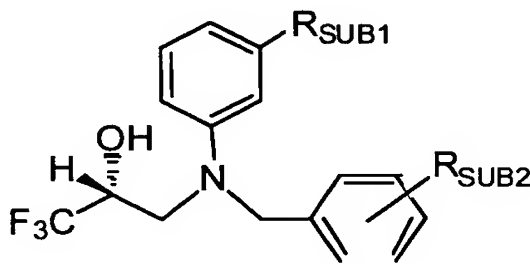
<u>Ex.</u> <u>No.</u>	<u>R<sub>SUB2</sub></u>	<u>Calculated</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>	<u>Observed</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>
732	3-iodo-benzyloxy	644.0533	644.0517
733	4-CF <sub>3</sub> S-benzyloxy	618.1161	618.1165
734	4-CF <sub>2</sub> HO-benzyloxy	584.1483	584.1480
735	4-fluoro-3-CF <sub>3</sub> -benzyloxy	604.1346	604.1336
736	2,3,5-trifluoro-benzyloxy	572.1284	572.1276
737	4-chloro-benzyloxy	552.1176	552.1188
738	2,5-difluoro-benzyloxy	554.1378	554.1350
739	3-chloro-2-fluoro-benzyloxy	570.1082	570.1069
740	2,4-(CF <sub>3</sub> ) <sub>2</sub> -benzyloxy	654.1314	654.1321
741	3,5-dichloro-benzyloxy	586.1787	586.1378
742	3-methoxy-benzyloxy	548.1672	548.1676
743	4-cyano-benzyloxy	543.1519	543.1517
744	4- <i>tert</i> -butyl-benzyloxy	574.2192	574.2163
745	isopropylthio	486.1338	486.1351
746	4-nitrophenylthio	565.1032	565.1034
747	4-acetylphenylthio	562.1287	562.1261
748	(4-chloro-thien-2-yl)-methylthio	574.0512	574.0523
749	4-methoxy-phenylamino	532.1597	532.1592
750	3-methoxy-phenylamino	532.1597	532.1593
751	4-chloro-phenylamino	536.1102	536.1125
752	4- <i>n</i> -propyl-phenylamino	544.1961	544.1959
753	3-cyano-phenylamino	527.1444	527.1448
754	3-CF <sub>3</sub> -benzyl	570.1413	570.1480
755	3-methyl-4-fluoro-benzyl	534.1679	534.1688
756	3-CF <sub>3</sub> -phenyl	556.1334	556.1339



Example Table 8 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl] amino]-1,1,1-trifluoro-2-propanols.

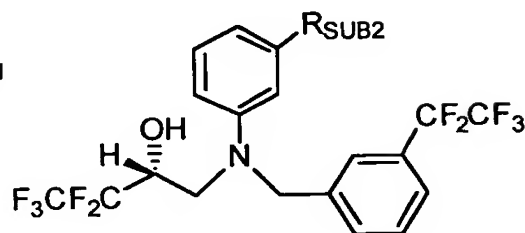
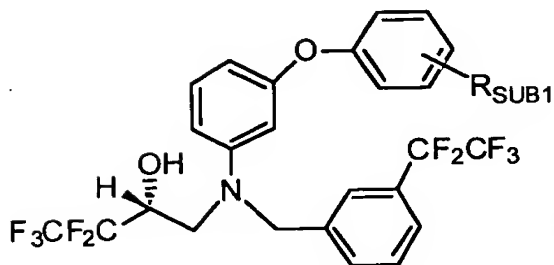
<u>Ex.</u> <u>No.</u>	<u>R<sub>SUB2</sub></u>	<u>Calculated</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>	<u>Observed</u> <u>Mass</u> <u>[M+H]<sup>+</sup></u>
757	2,4-dichloro-phenyl	556.0681	556.0651
758	3-methoxybenzyl	532.1723	532.1705
759	4-methoxyphenyl	518.1566	518.1533
760	3-chloro-4-fluoro-phenyl	540.0976	540.0957
761	4-fluoro-3-methyl-benzoyl	548.1410	548.1441
762	3-chlorobenzyl	536.1227	536.1218
763	3,4-dimethylbenzyl	530.1930	530.1887
764	3,5-dichlorobenzyl	570.0838	570.0801
765	2,3,4-trifluorophenyl	542.1177	542.1152
766	3-chloro-4-fluoro-benzyl	554.1133	554.1108
767	4-fluoro-3-methyl-phenyl	520.1523	520.1494
768	3-methyl-4-chloro-benzyl	550.1384	550.1380
769	2-methylpropanoyl	482.1566	482.1576
770	4-methylthiobenzyl	548.1494	548.1503
771	4-fluorophenyl	506.1366	506.1336
772	4-chlorophenyl	522.1071	522.1049
773	3-methoxyphenyl	518.1566	518.1544
774	4-methylbenzyl	516.1774	516.1769
775	1-hydroxy-2-methyl-propyl	484.1723	484.1725
776	benzyl	502.1617	502.1609
777	2-CF <sub>3</sub> -phenyl	556.1334	556.1286
778	3,4-dichlorophenyl	556.0681	556.0698
779	benzoyl	516.1410	516.1383
780	4-fluorobenzoyl	534.1315	534.1273
781	N-piperidiny	494.1804	494.1804
782	phenyl	488.1460	488.1457
783	thien-2-yl	494.1024	494.0987

Example Table 8 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)methyl] amino]-1,1,1-trifluoro-2-propanols.



<u>Ex. No.</u>	<u>R<sub>SUB1</sub></u>	<u>R<sub>SUB2</sub></u>	<u>Calculated Mass [M+H]<sup>+</sup></u>	<u>Observed Mass [M+H]<sup>+</sup></u>
784	phenoxy	3-cyclopentyl	456.2150	456.2143
785	phenoxy	3-isopropoxy	446.1943	446.1936
786	phenoxy	3-CF <sub>3</sub> S	488.1119	488.1116
787	4-F-phenoxy	3-CF <sub>3</sub> S	505.0946	505.0927
788	4-F-phenoxy	3- <i>sec</i> -butoxy	478.2005	478.1880
789	phenoxy	3-(CF <sub>3</sub> ) <sub>2</sub> COH-	554.1378	554.1385
790	4-CH <sub>3</sub> - phenoxy	3-CF <sub>3</sub> S	502.1275	502.1261
791	phenoxy	3-(2-furyl)	454.1630	454.1635
792	4-F-phenoxy	3-isopropoxy	464.1849	464.1867
793	phenoxy	3-isobutyl	444.2150	444.2157
794	phenoxy	3- <i>tert</i> -butoxy	460.2100	460.2103
795	4-F-phenoxy	3-CH <sub>3</sub> CH <sub>2</sub> O-	450.1692	450.1682
796	4-F-phenoxy	3-CF <sub>3</sub> O-	490.1253	490.1211
797	phenoxy	4-F-3-(2-furyl)-	472.1536	472.1530
798	4-F-phenoxy	3- <i>n</i> -propoxy-	464.1849	464.1820
799	4-F-phenoxy	3-cyclopentyloxy-	490.2005	490.1998
800	phenoxy	3-(3-furyl)-	454.1630	454.1646
801	4-F-phenoxy	3-cyclopropyl- methyleneoxy	476.1849	476.1857
802	phenoxy	3-CF <sub>3</sub> CH <sub>2</sub> O-	486.1504	486.1498

Example Table 9. (3*R*)-4-[*N*-(aryl)-[(aryl)methyl]amino]-  
1,1,1,2,2-pentafluoro-3-butanols.



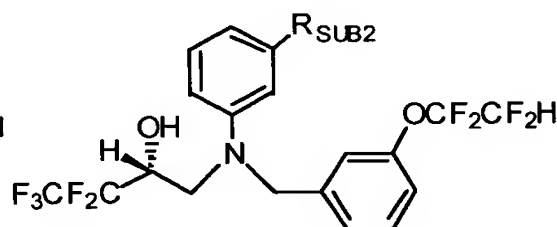
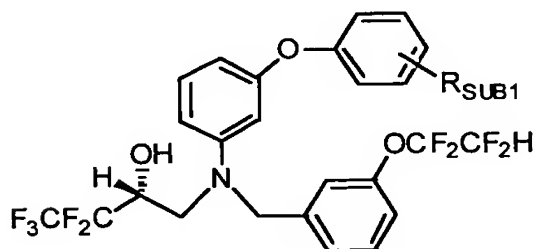
Ex. No.	R <sub>SUB1</sub>
803	3-isopropyl
804	2-Cl, 3-Cl
805	3-CF <sub>3</sub> O
806	4-F
807	4-CH <sub>3</sub>
808	2-F, 5-Br
809	4-Cl, 3-CH <sub>3</sub> CH <sub>2</sub>
810	3-CH <sub>3</sub> CH <sub>2</sub>
811	3-CH <sub>3</sub> , 5-CH <sub>3</sub>
812	3-(CH <sub>3</sub> ) <sub>3</sub> C
813	4-F, 3-CH <sub>3</sub>
814	3-Cl, 4-Cl
815	3,4-(CH <sub>2</sub> ) <sub>4</sub>
816	3-HCF <sub>2</sub> CF <sub>2</sub> O
817	3-CHF <sub>2</sub> O
818	3-(CH <sub>3</sub> ) <sub>2</sub> N
819	3-cyclopropyl
820	3-(2-furyl)
821	3-CF <sub>3</sub> CF <sub>2</sub>
822	4-NH <sub>2</sub>
823	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>
824	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O

Ex. No.	R <sub>SUB2</sub>
827	3-CF <sub>3</sub> O-benzyloxy
828	3-CF <sub>3</sub> -benzyloxy
829	3-F, 5-F-benzyloxy
830	cyclohexylmethylenoxy
831	benzyloxy
832	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
833	4-CF <sub>3</sub> O-benzyloxy
834	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy
835	isopropoxy
836	3-CF <sub>3</sub> -benzyl
837	isopropylthio
838	cyclopentoxy
839	3-Cl-5-pyridinyloxy
840	3-CF <sub>3</sub> S-benzyloxy
841	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
842	2-F, 3-CF <sub>3</sub> -benzyloxy
843	3-F, 5-CF <sub>3</sub> -benzyloxy
844	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy
845	1-phenylethoxy
846	4-F, 3-CH <sub>3</sub> -benzoyl
847	3-CF <sub>3</sub> -phenyl
848	4-CH <sub>3</sub> O-phenylamino

Example Table 9. (3*R*)-4-[*N*-(aryl)-[(aryl)methyl]amino]-1,1,1,2,2-pentafluoro-3-butanols (Continued).

Ex. No.	R <sub>SUB1</sub>
825	3-CF <sub>3</sub>
826	2-NO <sub>2</sub>

Ex. No.	R <sub>SUB2</sub>
849	cyclopropoxy
850	4-NO <sub>2</sub> -phenylthio



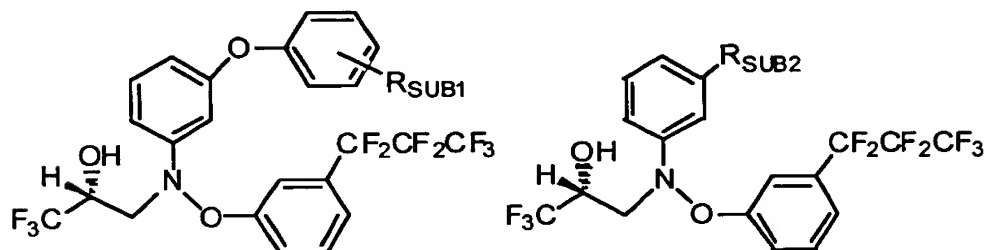
Ex. No.	R <sub>SUB1</sub>
851	3-isopropyl
852	2-Cl, 3-Cl
853	3-CF <sub>3</sub> O
854	4-F
855	4-CH <sub>3</sub>
856	2-F, 5-Br
857	4-Cl, 3-CH <sub>3</sub> CH <sub>2</sub>
858	3-CH <sub>3</sub> CH <sub>2</sub>
859	3-CH <sub>3</sub> , 5-CH <sub>3</sub>
860	3-(CH <sub>3</sub> ) <sub>3</sub> C
861	4-F, 3-CH <sub>3</sub>
862	3-Cl, 4-Cl
863	3,4-(CH <sub>2</sub> ) <sub>4</sub>
864	3-HCF <sub>2</sub> CF <sub>2</sub> O
865	3-CHF <sub>2</sub> O
866	3-(CH <sub>3</sub> ) <sub>2</sub> N
867	3-cyclopropyl
868	3-(2-furyl)

Ex. No.	R <sub>SUB2</sub>
875	3-CF <sub>3</sub> O-benzyloxy
876	3-CF <sub>3</sub> -benzyloxy
877	3-F, 5-F-benzyloxy
878	cyclohexylmethylenoxy
879	benzyloxy
880	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
881	4-CF <sub>3</sub> O-benzyloxy
882	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy
883	isopropoxy
884	3-CF <sub>3</sub> -benzyl
885	isopropylthio
886	cyclopentoxy
887	3-Cl-5-pyridinyloxy
888	3-CF <sub>3</sub> S-benzyloxy
889	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
890	2-F, 3-CF <sub>3</sub> -benzyloxy
891	3-F, 5-CF <sub>3</sub> -benzyloxy
892	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy

Example Table 9. (3*R*)-4-[*N*-(aryl)-[(aryl)methyl]amino]-1,1,1,2,2-pentafluoro-3-butanols (Continued).

<u>Ex.</u> <u>No.</u>	<u>R<sub>SUB1</sub></u>	<u>Ex.</u> <u>No.</u>	<u>R<sub>SUB2</sub></u>
869	3-CF <sub>3</sub> CF <sub>2</sub>	893	1-phenylethoxy
870	4-NH <sub>2</sub>	894	4-F, 3-CH <sub>3</sub> -benzoyl
871	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>	895	3-CF <sub>3</sub> -phenyl
872	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O	896	4-CH <sub>3</sub> O-phenylamino
873	3-CF <sub>3</sub>	897	cyclopropoxy
874	2-NO <sub>2</sub>	898	4-NO <sub>2</sub> -phenylthio

Example Table 10. Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)oxy]amino]-1,1,1-trifluoro-2-propanols.



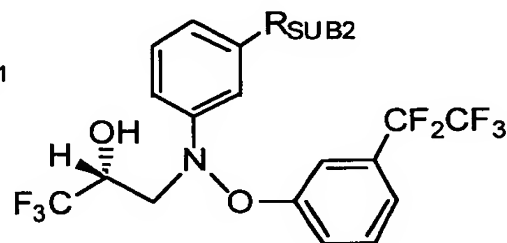
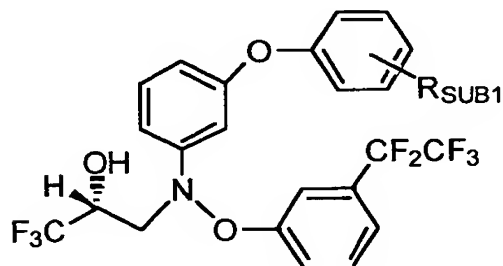
Ex. No.	R <sub>SUB1</sub>
899	3-isopropyl
900	2-Cl, 3-Cl
901	3-CF <sub>3</sub> O
902	4-F
903	4-CH <sub>3</sub>
904	2-F, 5-Br
905	4-Cl, 3-CH <sub>3</sub> CH <sub>2</sub>
906	3-CH <sub>3</sub> CH <sub>2</sub>
907	3-CH <sub>3</sub> , 5-CH <sub>3</sub>
908	3-(CH <sub>3</sub> ) <sub>3</sub> C
909	4-F, 3-CH <sub>3</sub>
910	3-Cl, 4-Cl
911	3,4-(CH <sub>2</sub> ) <sub>4</sub>
912	3-HCF <sub>2</sub> CF <sub>2</sub> O
913	3-CHF <sub>2</sub> O
914	3-(CH <sub>3</sub> ) <sub>2</sub> N
915	3-cyclopropyl
916	3-(2-furyl)
917	3-CF <sub>3</sub> CF <sub>2</sub>
918	4-NH <sub>2</sub>
919	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>
920	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O
921	3-CF <sub>3</sub>

Ex. No.	R <sub>SUB2</sub>
923	3-CF <sub>3</sub> O-benzyloxy
924	3-CF <sub>3</sub> -benzyloxy
925	3-F, 5-F-benzyloxy
926	cyclohexylmethylenoxy
927	benzyloxy
928	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
929	4-CF <sub>3</sub> O-benzyloxy
930	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy
931	isopropoxy
932	3-CF <sub>3</sub> -benzyl
933	isopropylthio
934	cyclopentoxy
935	3-Cl-5-pyridinyloxy
936	3-CF <sub>3</sub> S-benzyloxy
937	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
938	2-F, 3-CF <sub>3</sub> -benzyloxy
939	3-F, 5-CF <sub>3</sub> -benzyloxy
940	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy
941	1-phenylethoxy
942	4-F, 3-CH <sub>3</sub> -benzoyl
943	3-CF <sub>3</sub> -phenyl
944	4-CH <sub>3</sub> O-phenylamino
945	cyclopropoxy

Example Table 10 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)oxy]amino]-1,1,1-trifluoro-2-propanols.

<u>Ex. No.</u>	<u>R<sub>SUB1</sub></u>
922	2-NO <sub>2</sub>

<u>Ex. No.</u>	<u>R<sub>SUB2</sub></u>
946	4-NO <sub>2</sub> -phenylthio



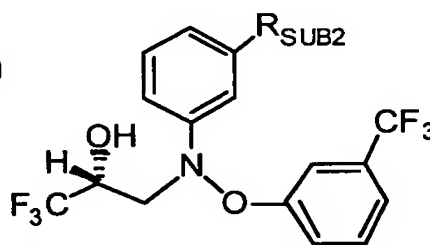
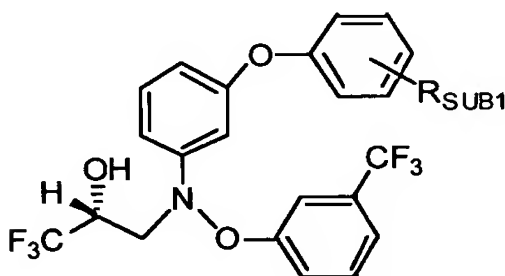
<u>Ex. No.</u>	<u>R<sub>SUB1</sub></u>
947	3-isopropyl
948	2-Cl, 3-Cl
949	3-CF <sub>3</sub> O
950	4-F
951	4-CH <sub>3</sub>
952	2-F, 5-Br
953	4-Cl, 3-CH <sub>3</sub> CH <sub>2</sub>
954	3-CH <sub>3</sub> CH <sub>2</sub>
955	3-CH <sub>3</sub> , 5-CH <sub>3</sub>
956	3-(CH <sub>3</sub> ) <sub>3</sub> C
957	4-F, 3-CH <sub>3</sub>
958	3-Cl, 4-Cl
959	3,4-(CH <sub>2</sub> ) <sub>4</sub>
960	3-HCF <sub>2</sub> CF <sub>2</sub> O
961	3-CHF <sub>2</sub> O
962	3-(CH <sub>3</sub> ) <sub>2</sub> N
963	3-cyclopropyl
964	3-(2-furyl)

<u>Ex. No.</u>	<u>R<sub>SUB2</sub></u>
971	3-CF <sub>3</sub> O-benzyloxy
972	3-CF <sub>3</sub> -benzyloxy
973	3-F, 5-F-benzyloxy
974	cyclohexylmethylenoxy
975	benzyloxy
976	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
977	4-CF <sub>3</sub> O-benzyloxy
978	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy
979	isopropoxy
980	3-CF <sub>3</sub> -benzyl
981	isopropylthio
982	cyclopentoxy
983	3-Cl-5-pyridinyloxy
984	3-CF <sub>3</sub> S-benzyloxy
985	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
986	2-F, 3-CF <sub>3</sub> -benzyloxy
987	3-F, 5-CF <sub>3</sub> -benzyloxy
988	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy

Example Table 10 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)oxy]amino]-1,1,1-trifluoro-2-propanols.

Ex. No.	R <sub>SUB1</sub>
965	3-CF <sub>3</sub> CF <sub>2</sub>
966	4-NH <sub>2</sub>
967	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>
968	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O
969	3-CF <sub>3</sub>
970	2-NO <sub>2</sub>

Ex. No.	R <sub>SUB2</sub>
989	1-phenylethoxy
990	4-F, 3-CH <sub>3</sub> -benzoyl
991	3-CF <sub>3</sub> -phenyl
992	4-CH <sub>3</sub> O-phenylamino
993	cyclopropoxy
994	4-NO <sub>2</sub> -phenylthio



Ex. No.	R <sub>SUB1</sub>
995	3-isopropyl
996	2-Cl, 3-Cl
997	3-CF <sub>3</sub> O
998	4-F
999	4-CH <sub>3</sub>
1000	2-F, 5-Br
1001	4-Cl, 3-CH <sub>3</sub> CH <sub>2</sub>
1002	3-CH <sub>3</sub> CH <sub>2</sub>
1003	3-CH <sub>3</sub> , 5-CH <sub>3</sub>
1004	3-(CH <sub>3</sub> ) <sub>3</sub> C
1005	4-F, 3-CH <sub>3</sub>
1006	3-Cl, 4-Cl
1007	3,4-(CH <sub>2</sub> ) <sub>4</sub>

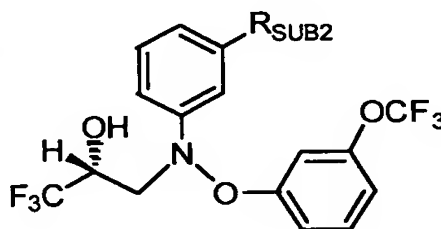
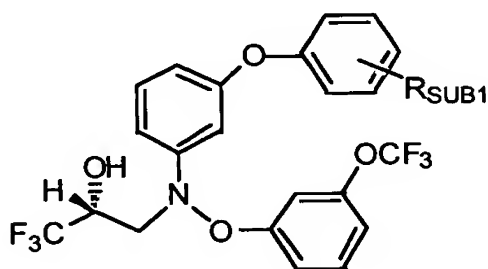
Ex. No.	R <sub>SUB2</sub>
1019	3-CF <sub>3</sub> O-benzyloxy
1020	3-CF <sub>3</sub> -benzyloxy
1021	3-F, 5-F-benzyloxy
1022	cyclohexylmethylenoxy
1023	benzyloxy
1024	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
1025	4-CF <sub>3</sub> O-benzyloxy
1026	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy
1027	isopropoxy
1028	3-CF <sub>3</sub> -benzyl
1029	isopropylthio
1030	cyclopentoxy
1031	3-Cl-5-pyridinyloxy



Example Table 10 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)oxy]amino]-1,1,1-trifluoro-2-propanols.

Ex. No.	R <sub>SUB1</sub>
1008	3-HCF <sub>2</sub> CF <sub>2</sub> O
1009	3-CHF <sub>2</sub> O
1010	3-(CH <sub>3</sub> ) <sub>2</sub> N
1011	3-cyclopropyl
1012	3-(2-furyl)
1013	3-CF <sub>3</sub> CF <sub>2</sub>
1014	4-NH <sub>2</sub>
1015	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>
1016	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O
1017	3-CF <sub>3</sub>
1018	2-NO <sub>2</sub>

Ex. No.	R <sub>SUB2</sub>
1032	3-CF <sub>3</sub> S-benzyloxy
1033	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
1034	2-F, 3-CF <sub>3</sub> -benzyloxy
1035	3-F, 5-CF <sub>3</sub> -benzyloxy
1036	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy
1037	1-phenylethoxy
1038	4-F, 3-CH <sub>3</sub> -benzoyl
1039	3-CF <sub>3</sub> -phenyl
1040	4-CH <sub>3</sub> O-phenylamino
1041	cyclopropoxy
1042	4-NO <sub>2</sub> -phenylthio

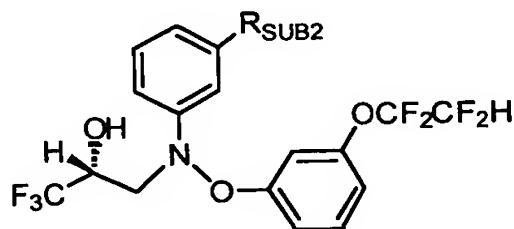
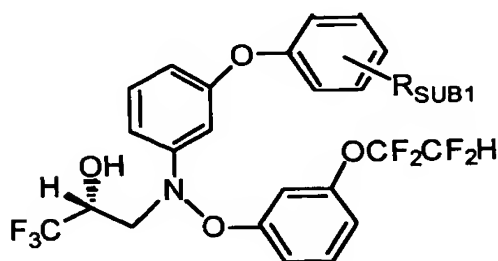


Ex. No.	R <sub>SUB1</sub>
1043	3-isopropyl
1044	2-Cl, 3-Cl
1045	3-CF <sub>3</sub> O
1046	4-F
1047	4-CH <sub>3</sub>
1048	2-F, 5-Br
1049	4-Cl, 3-CH <sub>3</sub> CH <sub>2</sub>
1050	3-CH <sub>3</sub> CH <sub>2</sub>

Ex. No.	R <sub>SUB2</sub>
1067	3-CF <sub>3</sub> O-benzyloxy
1068	3-CF <sub>3</sub> -benzyloxy
1069	3-F, 5-F-benzyloxy
1070	cyclohexylmethylenedioxy
1071	benzyloxy
1072	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
1073	4-CF <sub>3</sub> O-benzyloxy
1074	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy

Example Table 10 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)oxy]amino]-1,1,1-trifluoro-2-propanols.

Ex. No.	R <sub>SUB1</sub>	Ex. No.	R <sub>SUB2</sub>
1051	3-CH <sub>3</sub> , 5-CH <sub>3</sub>	1075	isopropoxy
1052	3-(CH <sub>3</sub> ) <sub>3</sub> C	1076	3-CF <sub>3</sub> -benzyl
1053	4-F, 3-CH <sub>3</sub>	1077	isopropylthio
1054	3-Cl, 4-Cl	1078	cyclopentoxy
1055	3,4-(CH <sub>2</sub> ) <sub>4</sub>	1079	3-Cl-5-pyridinyloxy
1056	3-HCF <sub>2</sub> CF <sub>2</sub> O	1080	3-CF <sub>3</sub> S-benzyloxy
1057	3-CHF <sub>2</sub> O	1081	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
1058	3-(CH <sub>3</sub> ) <sub>2</sub> N	1082	2-F, 3-CF <sub>3</sub> -benzyloxy
1059	3-cyclopropyl	1083	3-F, 5-CF <sub>3</sub> -benzyloxy
1060	3-(2-furyl)	1084	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy
1061	3-CF <sub>3</sub> CF <sub>2</sub>	1085	1-phenylethoxy
1062	4-NH <sub>2</sub>	1086	4-F, 3-CH <sub>3</sub> -benzoyl
1063	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>	1087	3-CF <sub>3</sub> -phenyl
1064	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O	1088	4-CH <sub>3</sub> O-phenylamino
1065	3-CF <sub>3</sub>	1089	cyclopropoxy
1066	2-NO <sub>2</sub>	1090	4-NO <sub>2</sub> -phenylthio

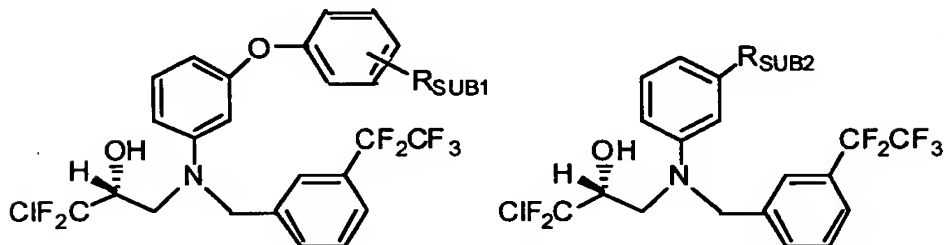


Ex. No.	R <sub>SUB1</sub>	Ex. No.	R <sub>SUB2</sub>
1091	3-isopropyl	1115	3-CF <sub>3</sub> O-benzyloxy
1092	2-Cl, 3-Cl	1116	3-CF <sub>3</sub> -benzyloxy
1093	3-CF <sub>3</sub> O	1117	3-F, 5-F-benzyloxy
1094	4-F	1118	cyclohexylmethylenoxy

Example Table 10 (continued). Substituted (2*R*)-3-[*N*-(aryl)-[(aryl)oxy]amino]-1,1,1-trifluoro-2-propanols.

<u>Ex. No.</u>	<u>R<sub>SUB1</sub></u>	<u>Ex. No.</u>	<u>R<sub>SUB2</sub></u>
1095	4-CH <sub>3</sub>	1119	benzyloxy
1096	2-F, 5-Br	1120	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
1097	4-Cl, 3-CH <sub>3</sub> CH <sub>2</sub>	1121	4-CF <sub>3</sub> O-benzyloxy
1098	3-CH <sub>3</sub> CH <sub>2</sub>	1122	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy
1099	3-CH <sub>3</sub> , 5-CH <sub>3</sub>	1123	isopropoxy
1100	3-(CH <sub>3</sub> ) <sub>3</sub> C	1124	3-CF <sub>3</sub> -benzyl
1101	4-F, 3-CH <sub>3</sub>	1125	isopropylthio
1102	3-Cl, 4-Cl	1126	cyclopentoxy
1103	3,4-(CH <sub>2</sub> ) <sub>4</sub>	1127	3-Cl-5-pyridinyloxy
1104	3-HCF <sub>2</sub> CF <sub>2</sub> O	1128	3-CF <sub>3</sub> S-benzyloxy
1105	3-CHF <sub>2</sub> O	1129	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
1106	3-(CH <sub>3</sub> ) <sub>2</sub> N	1130	2-F, 3-CF <sub>3</sub> -benzyloxy
1107	3-cyclopropyl	1131	3-F, 5-CF <sub>3</sub> -benzyloxy
1108	3-(2-furyl)	1132	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy
1109	3-CF <sub>3</sub> CF <sub>2</sub>	1133	1-phenylethoxy
1110	4-NH <sub>2</sub>	1134	4-F, 3-CH <sub>3</sub> -benzoyl
1111	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>	1135	3-CF <sub>3</sub> -phenyl
1112	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O	1136	4-CH <sub>3</sub> O-phenylamino
1113	3-CF <sub>3</sub>	1137	cyclopropoxy
1114	2-NO <sub>2</sub>	1138	4-NO <sub>2</sub> -phenylthio

Example Table 11. (2*R*)-3-[*N*-(aryl)-[(aryl)methyl]amino]-1,1-difluoro-1-chloro-2-propanols.



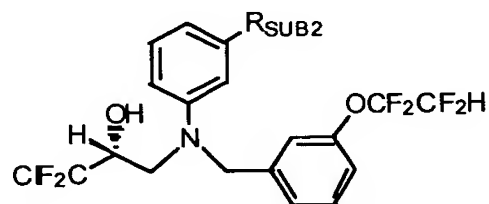
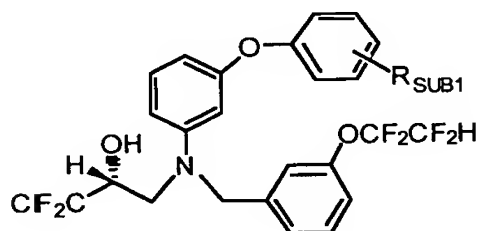
Ex. No.	R <sub>SUB1</sub>
1139	3-isopropyl
1140	2-Cl, 3-Cl
1141	3-CF <sub>3</sub> O
1142	4-F
1143	4-CH <sub>3</sub>
1144	2-F, 5-Br
1145	4-Cl, 3-CH <sub>3</sub> CH <sub>2</sub>
1146	3-CH <sub>3</sub> CH <sub>2</sub>
1147	3-CH <sub>3</sub> , 5-CH <sub>3</sub>
1148	3-(CH <sub>3</sub> ) <sub>3</sub> C
1149	4-F, 3-CH <sub>3</sub>
1150	3-Cl, 4-Cl
1151	3,4-(CH <sub>2</sub> ) <sub>4</sub>
1152	3-HCF <sub>2</sub> CF <sub>2</sub> O
1153	3-CHF <sub>2</sub> O
1154	3-(CH <sub>3</sub> ) <sub>2</sub> N
1155	3-cyclopropyl
1156	3-(2-furyl)
1157	3-CF <sub>3</sub> CF <sub>2</sub>
1158	4-NH <sub>2</sub>
1159	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>
1160	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O
1161	3-CF <sub>3</sub>

Ex. No.	R <sub>SUB2</sub>
1163	3-CF <sub>3</sub> O-benzyloxy
1164	3-CF <sub>3</sub> -benzyloxy
1165	3-F, 5-F-benzyloxy
1166	cyclohexylmethylenoxy
1167	benzyloxy
1168	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
1169	4-CF <sub>3</sub> O-benzyloxy
1170	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy
1171	isopropoxy
1172	3-CF <sub>3</sub> -benzyl
1173	isopropylthio
1174	cyclopentoxy
1175	3-Cl-5-pyridinyloxy
1176	3-CF <sub>3</sub> S-benzyloxy
1177	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
1178	2-F, 3-CF <sub>3</sub> -benzyloxy
1179	3-F, 5-CF <sub>3</sub> -benzyloxy
1180	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy
1181	1-phenylethoxy
1182	4-F, 3-CH <sub>3</sub> -benzoyl
1183	3-CF <sub>3</sub> -phenyl
1184	4-CH <sub>3</sub> O-phenylamino
1185	cyclopropoxy

Example Table 11 (continued). (2*R*)-3-[*N*-(aryl)-[(aryl)methyl]amino]-1,1-difluoro-1-chloro-2-propanols.

Ex. No.	<u>R<sub>SUB1</sub></u>
1162	2-NO <sub>2</sub>

Ex. No.	<u>R<sub>SUB2</sub></u>
1186	4-NO <sub>2</sub> -phenylthio



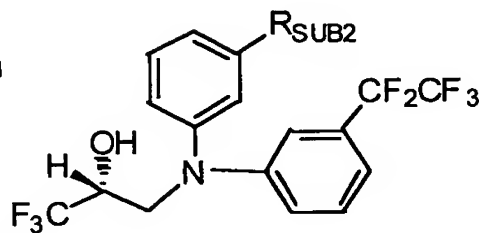
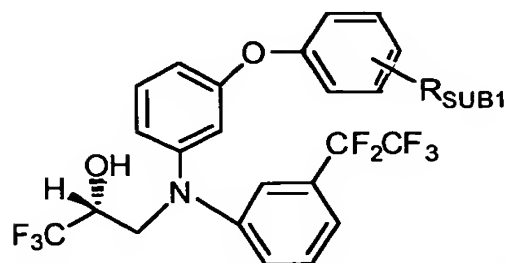
Ex. No.	<u>R<sub>SUB1</sub></u>
1187	3-isopropyl
1188	2-Cl, 3-Cl
1189	3-CF <sub>3</sub> O
1190	4-F
1191	4-CH <sub>3</sub>
1192	2-F, 5-Br
1193	4-Cl, 3-CH <sub>3</sub> CH <sub>2</sub>
1194	3-CH <sub>3</sub> CH <sub>2</sub>
1195	3-CH <sub>3</sub> , 5-CH <sub>3</sub>
1196	3-(CH <sub>3</sub> ) <sub>3</sub> C
1197	4-F, 3-CH <sub>3</sub>
1198	3-Cl, 4-Cl
1199	3,4-(CH <sub>2</sub> ) <sub>4</sub>
1200	3-HCF <sub>2</sub> CF <sub>2</sub> O
1201	3-CHF <sub>2</sub> O
1202	3-(CH <sub>3</sub> ) <sub>2</sub> N
1203	3-cyclopropyl
1204	3-(2-furyl)
1205	3-CF <sub>3</sub> CF <sub>2</sub>

Ex. No.	<u>R<sub>SUB2</sub></u>
1211	3-CF <sub>3</sub> O-benzyloxy
1212	3-CF <sub>3</sub> -benzyloxy
1213	3-F, 5-F-benzyloxy
1214	cyclohexylmethylenoxy
1215	benzyloxy
1216	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
1217	4-CF <sub>3</sub> O-benzyloxy
1218	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy
1219	isopropoxy
1220	3-CF <sub>3</sub> -benzyl
1221	isopropylthio
1222	cyclopentoxy
1223	3-Cl-5-pyridinyloxy
1224	3-CF <sub>3</sub> S-benzyloxy
1225	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
1226	2-F, 3-CF <sub>3</sub> -benzyloxy
1227	3-F, 5-CF <sub>3</sub> -benzyloxy
1228	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy
1229	1-phenylethoxy

Example Table 11 (continued). (2*R*)-3-[*N*-(aryl)-[(aryl)methyl]amino]-1,1-difluoro-1-chloro-2-propanols.

<u>Ex. No.</u>	<u>R<sub>SUB1</sub></u>
1206	4-NH <sub>2</sub>
1207	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>
1208	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O
1209	3-CF <sub>3</sub>
1210	2-NO <sub>2</sub>

<u>Ex. No.</u>	<u>R<sub>SUB2</sub></u>
1230	4-F, 3-CH <sub>3</sub> -benzoyl
1231	3-CF <sub>3</sub> -phenyl
1232	4-CH <sub>3</sub> O-phenylamino
1233	cyclopropoxy
1234	4-NO <sub>2</sub> -phenylthio

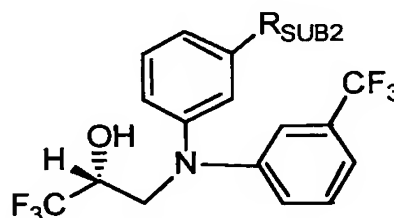
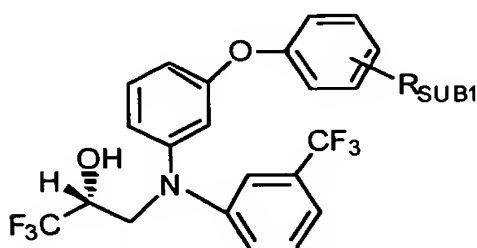
Example Table 12. (2*R*)-3-[*N,N'*-(diaryl)amino]-1,1,1-trifluoro-2-propanols.

Ex. No.	R <sub>SUB1</sub>
1235	3-isopropyl
1236	2-Cl, 3-Cl
1237	3-CF <sub>3</sub> O
1238	4-F
1239	4-CH <sub>3</sub>
1240	2-F, 5-Br
1241	4-Cl, 3-CH <sub>3</sub> CH <sub>2</sub>
1242	3-CH <sub>3</sub> CH <sub>2</sub>
1243	3-CH <sub>3</sub> , 5-CH <sub>3</sub>
1244	3-(CH <sub>3</sub> ) <sub>3</sub> C
1245	4-F, 3-CH <sub>3</sub>
1246	3-Cl, 4-Cl
1247	3,4-(CH <sub>2</sub> ) <sub>4</sub>
1248	3-HCF <sub>2</sub> CF <sub>2</sub> O
1249	3-CHF <sub>2</sub> O
1250	3-(CH <sub>3</sub> ) <sub>2</sub> N
1251	3-cyclopropyl
1252	3-(2-furyl)
1253	3-CF <sub>3</sub> CF <sub>2</sub>
1254	4-NH <sub>2</sub>
1255	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>
1256	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O
1257	3-CF <sub>3</sub>

Ex. No.	R <sub>SUB2</sub>
1259	3-CF <sub>3</sub> O-benzyloxy
1260	3-CF <sub>3</sub> -benzyloxy
1261	3-F, 5-F-benzyloxy
1262	cyclohexylmethyleneoxy
1263	benzyloxy
1264	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
1265	4-CF <sub>3</sub> O-benzyloxy
1266	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy
1267	isopropoxy
1268	3-CF <sub>3</sub> -benzyl
1269	isopropylthio
1270	cyclopentoxy
1271	3-Cl-5-pyridinyloxy
1272	3-CF <sub>3</sub> S-benzyloxy
1273	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
1274	2-F, 3-CF <sub>3</sub> -benzyloxy
1275	3-F, 5-CF <sub>3</sub> -benzyloxy
1276	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy
1277	1-phenylethoxy
1278	4-F, 3-CH <sub>3</sub> -benzoyl
1279	3-CF <sub>3</sub> -phenyl
1280	4-CH <sub>3</sub> O-phenylamino
1281	cyclopropoxy

Example Table 12 (continued). (2*R*)-3-[*N,N'*-(diaryl)amino]-1,1,1-trifluoro-2-propanols.

<u>Ex. No.</u>	<u>R<sub>SUB1</sub></u>	<u>Ex. No.</u>	<u>R<sub>SUB2</sub></u>
1258	2-NO <sub>2</sub>	1282	4-NO <sub>2</sub> -phenylthio



<u>Ex. No.</u>	<u>R<sub>SUB1</sub></u>
1283	3-isopropyl
1284	2-Cl, 3-Cl
1285	3-CF <sub>3</sub> O
1286	4-F
1287	4-CH <sub>3</sub>
1288	2-F, 5-Br
1289	4-Cl, 3-CH <sub>3</sub> CH <sub>2</sub>
1290	3-CH <sub>3</sub> CH <sub>2</sub>
1291	3-CH <sub>3</sub> , 5-CH <sub>3</sub>
1292	3-(CH <sub>3</sub> ) <sub>3</sub> C
1293	4-F, 3-CH <sub>3</sub>
1294	3-Cl, 4-Cl
1295	3,4-(CH <sub>2</sub> ) <sub>4</sub>
1296	3-HCF <sub>2</sub> CF <sub>2</sub> O
1297	3-CHF <sub>2</sub> O
1298	3-(CH <sub>3</sub> ) <sub>2</sub> N
1299	3-cyclopropyl
1300	3-(2-furyl)

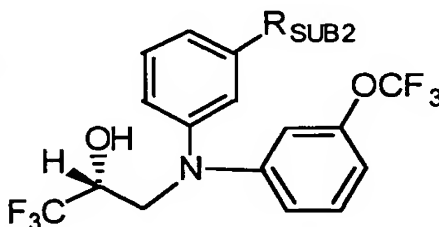
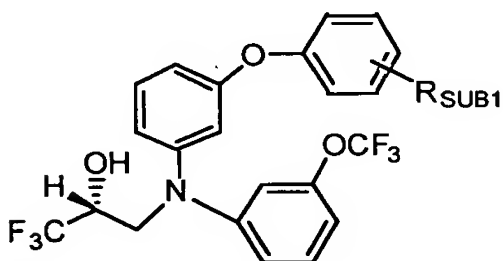
<u>Ex. No.</u>	<u>R<sub>SUB2</sub></u>
1307	3-CF <sub>3</sub> O-benzyloxy
1308	3-CF <sub>3</sub> -benzyloxy
1309	3-F, 5-F-benzyloxy
1310	cyclohexylmethylenoxy
1311	benzyloxy
1312	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
1313	4-CF <sub>3</sub> O-benzyloxy
1314	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy
1315	isopropoxy
1316	3-CF <sub>3</sub> -benzyl
1317	isopropylthio
1318	cyclopentoxy
1319	3-Cl-5-pyridinyloxy
1320	3-CF <sub>3</sub> S-benzyloxy
1321	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
1322	2-F, 3-CF <sub>3</sub> -benzyloxy
1323	3-F, 5-CF <sub>3</sub> -benzyloxy
1324	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy



Example Table 12 (continued). (2*R*)-3-[*N,N'*-(diaryl)amino]-1,1,1-trifluoro-2-propanols.

<u>Ex. No.</u>	<u>R<sub>SUB1</sub></u>
1301	3-CF <sub>3</sub> CF <sub>2</sub>
1302	4-NH <sub>2</sub>
1303	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>
1304	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O
1305	3-CF <sub>3</sub>
1306	2-NO <sub>2</sub>

<u>Ex. No.</u>	<u>R<sub>SUB2</sub></u>
1325	1-phenylethoxy
1326	4-F, 3-CH <sub>3</sub> -benzoyl
1327	3-CF <sub>3</sub> -phenyl
1328	4-CH <sub>3</sub> O-phenylamino
1329	cyclopropoxy
1330	4-NO <sub>2</sub> -phenylthio



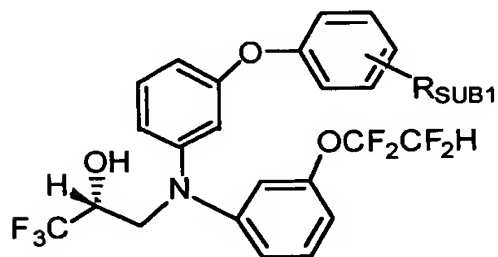
<u>Ex. No.</u>	<u>R<sub>SUB1</sub></u>
1331	3-isopropyl
1332	2-Cl, 3-Cl
1333	3-CF <sub>3</sub> O
1334	4-F
1335	4-CH <sub>3</sub>
1336	2-F, 5-Br
1337	4-Cl, 3-CH <sub>3</sub> CH <sub>2</sub>
1338	3-CH <sub>3</sub> CH <sub>2</sub>
1339	3-CH <sub>3</sub> , 5-CH <sub>3</sub>
1340	3-(CH <sub>3</sub> ) <sub>3</sub> C
1341	4-F, 3-CH <sub>3</sub>
1342	3-Cl, 4-Cl
1343	3,4-(CH <sub>2</sub> ) <sub>4</sub>

<u>Ex. No.</u>	<u>R<sub>SUB2</sub></u>
1355	3-CF <sub>3</sub> O-benzyloxy
1356	3-CF <sub>3</sub> -benzyloxy
1357	3-F, 5-F-benzyloxy
1358	cyclohexylmethylenoxy
1359	benzyloxy
1360	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
1361	4-CF <sub>3</sub> O-benzyloxy
1362	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy
1363	isopropoxy
1364	3-CF <sub>3</sub> -benzyl
1365	isopropylthio
1366	cyclopentoxy
1367	3-Cl-5-pyridinyloxy

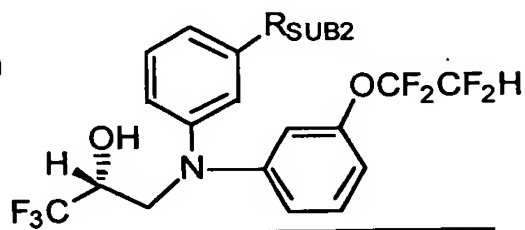
Example Table 12 (continued). (2*R*)-3-[*N,N'*-(diaryl)amino]-1,1,1-trifluoro-2-propanols.

Ex. No.	R <sub>SUB1</sub>
1344	3-HCF <sub>2</sub> CF <sub>2</sub> O
1345	3-CHF <sub>2</sub> O
1346	3-(CH <sub>3</sub> ) <sub>2</sub> N
1347	3-cyclopropyl
1348	3-(2-furyl)
1349	3-CF <sub>3</sub> CF <sub>2</sub>
1350	4-NH <sub>2</sub>
1351	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>
1352	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O
1353	3-CF <sub>3</sub>
1354	2-NO <sub>2</sub>

Ex. No.	R <sub>SUB2</sub>
1368	3-CF <sub>3</sub> S-benzyloxy
1369	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
1370	2-F, 3-CF <sub>3</sub> -benzyloxy
1371	3-F, 5-CF <sub>3</sub> -benzyloxy
1372	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy
1373	1-phenylethoxy
1374	4-F, 3-CH <sub>3</sub> -benzoyl
1375	3-CF <sub>3</sub> -phenyl
1376	4-CH <sub>3</sub> O-phenylamino
1377	cyclopropoxy
1378	4-NO <sub>2</sub> -phenylthio



Ex. No.	R <sub>SUB1</sub>
1379	3-isopropyl
1380	2-Cl, 3-Cl
1381	3-CF <sub>3</sub> O
1382	4-F
1383	4-CH <sub>3</sub>
1384	2-F, 5-Br
1385	4-Cl, 3-CH <sub>3</sub> CH <sub>2</sub>
1386	3-CH <sub>3</sub> CH <sub>2</sub>



Ex. No.	R <sub>SUB2</sub>
1403	3-CF <sub>3</sub> O-benzyloxy
1404	3-CF <sub>3</sub> -benzyloxy
1405	3-F, 5-F-benzyloxy
1406	cyclohexylmethylenedioxy
1407	benzyloxy
1408	3-CF <sub>3</sub> , 5-CF <sub>3</sub> -benzyloxy
1409	4-CF <sub>3</sub> O-benzyloxy
1410	4-CH <sub>3</sub> CH <sub>2</sub> -benzyloxy

Example Table 12 (continued). (2*R*)-3-[*N,N'*-(diaryl)amino]-1,1,1-trifluoro-2-propanols.

<u>Ex. No.</u>	<u>R<sub>SUB1</sub></u>	<u>Ex. No.</u>	<u>R<sub>SUB2</sub></u>
1387	3-CH <sub>3</sub> , 5-CH <sub>3</sub>	1411	isopropoxy
1388	3-(CH <sub>3</sub> ) <sub>3</sub> C	1412	3-CF <sub>3</sub> -benzyl
1389	4-F, 3-CH <sub>3</sub>	1413	isopropylthio
1390	3-Cl, 4-Cl	1414	cyclopentoxy
1391	3,4-(CH <sub>2</sub> ) <sub>4</sub>	1415	3-Cl-5-pyridinyloxy
1392	3-HCF <sub>2</sub> CF <sub>2</sub> O	1416	3-CF <sub>3</sub> S-benzyloxy
1393	3-CHF <sub>2</sub> O	1417	3-CH <sub>3</sub> , 4-CH <sub>3</sub> -benzyloxy
1394	3-(CH <sub>3</sub> ) <sub>2</sub> N	1418	2-F, 3-CF <sub>3</sub> -benzyloxy
1395	3-cyclopropyl	1419	3-F, 5-CF <sub>3</sub> -benzyloxy
1396	3-(2-furyl)	1420	4-(CH <sub>3</sub> ) <sub>2</sub> CH-benzyloxy
1397	3-CF <sub>3</sub> CF <sub>2</sub>	1421	1-phenylethoxy
1398	4-NH <sub>2</sub>	1422	4-F, 3-CH <sub>3</sub> -benzoyl
1399	3-CH <sub>3</sub> , 4-CH <sub>3</sub> , 5-CH <sub>3</sub>	1423	3-CF <sub>3</sub> -phenyl
1400	4-CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> O	1424	4-CH <sub>3</sub> O-phenylamino
1401	3-CF <sub>3</sub>	1425	cyclopropoxy
1402	2-NO <sub>2</sub>	1426	4-NO <sub>2</sub> -phenylthio

**BIOASSAYS****CETP Activity *In Vitro*****ASSAY OF CETP INHIBITION USING PURIFIED COMPONENTS  
(RECONSTITUTED BUFFER ASSAY)**

- 5           The ability of compounds to inhibit CETP activity was assessed using an *in vitro* assay that measured the rate of transfer of radiolabeled cholesteryl ester ( $[^3\text{H}]\text{CE}$ ) from HDL donor particles to LDL acceptor particles. Details of the assay are provided by Glenn, K. C. et al. (Glenn and Melton, "Quantification of Cholesteryl Ester Transfer Protein (CETP): A) CETP Activity and B)
- 10   Immunochemical Assay of CETP Protein," *Meth. Enzymol.*, 263, 339-351 (1996)). Human recombinant CETP can be obtained from the serum-free conditioned medium of CHO cells transfected with a cDNA for CETP and purified as described by Wang, S. et al. (*J. Biol. Chem.* 267, 17487-17490 (1992)). To measure CETP activity,  $[^3\text{H}]\text{CE}$ -labeled-HDL, LDL, CETP and
- 15   assay buffer (50 mM tris(hydroxymethyl)aminomethane, pH 7.4; 150 mM sodium chloride; 2 mM ethylenediamine-tetraacetic acid (EDTA); 1% bovine serum albumin) were incubated in a final volume of 200  $\mu\text{L}$ , for 2 hours at 37  $^{\circ}\text{C}$  in 96 well plates. Inhibitors were included in the assay by diluting from a 10 mM DMSO stock solution into 16% (v/v) aqueous DMSO so that the final
- 20   concentration of inhibitor was 800  $\mu\text{M}$ . The inhibitors were then diluted 1:1 with CETP in assay buffer, and then 25  $\mu\text{L}$  of that solution was mixed with 175  $\mu\text{L}$  of lipoprotein pool for assay. Following incubation, LDL was differentially precipitated by the addition of 50  $\mu\text{L}$  of 1% (w/v) dextran sulfate/0.5 M magnesium chloride, mixed by vortex, and incubated at room temperature for 10
- 25   minutes. A portion of the solution (200  $\mu\text{L}$ ) was transferred to a filter plate (Millipore). After filtration, the radioactivity present in the precipitated LDL was measured by liquid scintillation counting. Correction for non-specific transfer or precipitation was made by including samples that do not contain

CETP. The rate of [ $^3\text{H}$ ]CE transfer using this assay was linear with respect to time and CETP concentration, up to 25-30% of [ $^3\text{H}$ ]CE transferred.

The potency of test compounds was determined by performing the above described assay in the presence of varying concentrations of the test compounds and determining the concentration required for 50% inhibition of transfer of [ $^3\text{H}$ ]CE from HDL to LDL. This value was defined as the  $\text{IC}_{50}$ . The  $\text{IC}_{50}$  values determined from this assay are accurate when the  $\text{IC}_{50}$  is greater than 10 nM. In the case where compounds have greater inhibitory potency, accurate measurements of  $\text{IC}_{50}$  may be determined using longer incubation times (up to 18 hours) and lower final concentrations of CETP ( $< 50$  nM).

Examples of  $\text{IC}_{50}$  values determined by these methods are summarized in Table 9.

#### ASSAY OF CETP INHIBITION IN HUMAN PLASMA

Blood was obtained from healthy volunteers, recruited from the personnel of Monsanto Company, Saint Louis, MO. Blood was collected in tubes containing EDTA (EDTA plasma pool). The EDTA human plasma pool, previously stored at  $-20^\circ\text{C}$ , was thawed at room temperature and centrifuged for 5 minutes to remove any particulate matter. Tritiated HDL, radiolabeled in the cholesteryl ester moiety ([ $^3\text{H}$ ]CE-HDL) as described by Morton and Zilversmit (J. Biol. Chem., 256, 11992-95 (1981)), was added to the plasma to a final concentration of 25  $\mu\text{g/mL}$  cholesterol. Equal volumes (396  $\mu\text{L}$ ) of the plasma containing the [ $^3\text{H}$ ]CE-HDL were added by pipette into micro tubes (Titertube<sup>®</sup>, Bio-Rad laboratories, Hercules, CA). Inhibitor compounds, dissolved as 20-50 mM stock solutions in DMSO, were serially diluted in DMSO (or an alternative solvent in some cases, such as dimethylformamide or ethanol). Four  $\mu\text{L}$  of each of the serial dilutions of inhibitor compounds or DMSO alone were then added to each of the tubes containing plasma (396  $\mu\text{L}$ ). After mixing, triplicate aliquots (100  $\mu\text{L}$ ) from each plasma tube were then transferred to wells of 96-well round-bottomed polystyrene microtiter plates (Corning, Corning, NY). Plates were

sealed with plastic film and incubated at 37 °C for 4 hours. "Test" samples contained plasma with dilutions of inhibitor compounds. "Control" samples contained plasma with DMSO diluted to the same concentration as the test samples, but without inhibitor. "Blank" samples were prepared as "control" samples, but were left in the micro tubes at 4 °C for the 4 hour incubation and were then added to the microtiter wells at the end of the incubation period. VLDL and LDL were precipitated by the addition of 10 µL of precipitating reagent (1% (w/v) dextran sulfate (Dextralip50)/0.5 M magnesium chloride, pH 7.4) to all wells. The wells were mixed on a plate mixer and then incubated at ambient temperature for 10 min. The plates were then centrifuged at 1000 x g for 30 min at 10 °C. The supernatants (50 µL) from each well were then transferred to Picoplate™ 96 plate wells (Packard, Meriden, CT) containing Microscint™-40 (Packard, Meriden, CT). The plates were heat-sealed (TopSeal™-P, Packard, Meriden, CT) according to the manufacturer's directions and mixed for 30 min. Radioactivity was measured on a microplate scintillation counter (TopCount, Packard, Meriden, CT). The maximum percentage transfer in the control wells (% transfer) was determined using the following equation:

$$\% \text{ Transfer} = \frac{[\text{dpm}_{\text{blank}} - \text{dpm}_{\text{control}}] \times 100}{\text{dpm}_{\text{blank}}}$$

The percentage of transfer relative to the control (% control) was determined in the wells containing inhibitor compounds was determined as follows:

$$\% \text{ Control} = \frac{[\text{dpm}_{\text{blank}} - \text{dpm}_{\text{test}}] \times 100}{\text{dpm}_{\text{blank}} - \text{dpm}_{\text{control}}}$$

IC<sub>50</sub> values were then calculated from plots of % control versus concentration

of inhibitor compound. IC<sub>50</sub> values were determined as the concentration of inhibitor compound inhibiting transfer of [<sup>3</sup>H]CE from the supernatant [<sup>3</sup>H]CE-HDL to the precipitated VLDL and LDL by 50% compared to the transfer obtained in the control wells.

- 5           Examples of plasma IC<sub>50</sub> values determined by these methods are summarized in Table 10.

#### ASSAY OF CETP INHIBITION *IN VIVO*.

- 10           Inhibition of CETP activity by a test compound can be determined by administering the compound to an animal by intravenous injection or oral gavage, measuring the amount of transfer of tritium-labeled cholesteryl ester ([<sup>3</sup>H]CE) from HDL to VLDL and LDL particles, and comparing this amount of transfer with the amount of transfer observed in control animals.

- 15           Male golden Syrian hamsters were maintained on a diet of chow containing 0.24% cholesterol for at least two weeks prior to the study. For animals receiving intravenous dosing immediately before the experiment, animals were anesthetized with pentobarbital. Anesthesia was maintained throughout the experiment. In-dwelling catheters were inserted into the jugular vein and carotid artery. At the start of the experiment all animals received 0.2 mL of a solution containing [<sup>3</sup>H]CE-HDL into the jugular vein. [<sup>3</sup>H]CE-HDL  
20           is a preparation of human HDL containing tritium-labeled cholesteryl ester, and was prepared according to the method of Glenn et al. (*Meth. Enzymol.*, 263, 339-351 (1996)). Test compound was dissolved as a 80 mM stock solution in vehicle (2% ethanol: 98% PEG 400, Sigma Chemical Company, St. Louis, Missouri, USA) and administered either by bolus injection or by continuous infusion. Two  
25           minutes after the [<sup>3</sup>H]CE-HDL dose was administered, animals received 0.1 mL of the test solution injected into the jugular vein. Control animals received 0.1 mL of the intravenous vehicle solution without test compound. After 5 minutes, the first blood samples (0.5 mL) were taken from the carotid artery and collected in standard microtainer tubes containing ethylenediamine tetraacetic acid. Saline

(0.5 mL) was injected to flush the catheter and replace blood volume.

Subsequent blood samples were taken at two hours and four hours by the same method. Blood samples were mixed well and kept on ice until the completion of the experiment. Plasma was obtained by centrifugation of the blood samples at 4 °C. The plasma (50 µL) was treated with 5 µL of precipitating reagent (dextran sulfate, 10 g/L; 0.5 M magnesium chloride) to remove VLDL/LDL. After centrifugation, the resulting supernatant (25 µL) containing the HDL was analyzed for radioactivity using a liquid scintillation counter.

The percentage [<sup>3</sup>H]CE transferred from HDL to LDL and VLDL (% transfer) was calculated based on the total radioactivity in equivalent plasma samples before precipitation. Typically, the amount of transfer from HDL to LDL and VLDL in control animals was 20% to 35% after 4 hours. The polyethylene glycol vehicle was determined to have no effect on CETP activity in this model.

Alternatively, conscious, non-anesthetized animals received an oral gavage dose of test compound as a suspension in 0.1% methyl cellulose in water. At a time determined for each compound at which plasma levels of the test substance reached their peak ( $C_{max}$ ) after oral dosing, the animals were anesthetized with pentobarbital and then dosed with 0.2 mL of a solution containing [<sup>3</sup>H]CE-HDL into the jugular vein as described above. Control animals received 0.25 mL of the vehicle solution without test compound by oral gavage. After 4 hours, the animals were sacrificed, blood samples were collected, and the percentage [<sup>3</sup>H]CE transferred from HDL to LDL and VLDL (% transfer) assayed, as described above. The aqueous methyl cellulose vehicle was determined to have no effect on CETP activity in this model. Results from testing in this model are summarized in Table 11.

Alternatively, inhibition of CETP activity by a test compound was determined by administering the compound to mice which have been selected for expression of human CETP (hCETP) by transgenic manipulation (hCETP mice). Test compounds were administered by intravenous injection, or oral gavage and



the amount of transfer of tritium-labeled cholesteryl ester ( $[^3\text{H}]\text{CE}$ ) from HDL to VLDL and LDL particles was determined, and compared to the amount of transfer observed in control animals. C57Bl/6 mice that were homozygous for the hCETP gene were maintained on a high fat chow diet, such as TD 88051, as described by Nishina et al. (J Lipid Res., 31, 859-869 (1990)) for at least two weeks prior to the study. Mice received an oral gavage dose of test compound as a suspension in 0.1% methyl cellulose in water or an intravenous bolus injection of test compound in 10% ethanol and 90% polyethylene glycol. Control animals received the vehicle solution without test compound by oral gavage or by an intravenous bolus injection. At the start of the experiment all animals received 0.05 mL of a solution containing  $[^3\text{H}]\text{CE}$ -HDL into the tail vein.  $[^3\text{H}]\text{CE}$ -HDL is a preparation of human HDL containing tritium-labeled cholesteryl ester, and was prepared according to the method of Glenn et al. (*Meth. Enzymol.*, 263, 339-351 (1996)). After 30 minutes, the animals were exsanguinated and blood collected in standard microtainer tubes containing ethylenediamine tetraacetic acid. Blood samples were mixed well and kept on ice until the completion of the experiment. Plasma was obtained by centrifugation of the blood samples at 4 °C. The plasma was separated and analyzed by gel filtration chromatography and the relative proportion of  $[^3\text{H}]\text{CE}$  in the VLDL, LDL and HDL regions was determined.

The percentage  $[^3\text{H}]\text{CE}$  transferred from HDL to LDL and VLDL (% transfer) was calculated based on the total radioactivity in equivalent plasma samples before precipitation. Typically, the amount of transfer from HDL to LDL and VLDL in control animals was 20% to 35% after 30 min. The polyethylene glycol and the aqueous methyl cellulose vehicles were determined to have no effect on CETP activity in this model. Results from testing in this model are summarized in Table 12.

#### **ASSAY OF PLASMA HDL ELEVATION *IN VIVO*.**

Syrian Golden hamsters were made hypercholesterolemic by feeding cholesterol supplemented chow for a minimum of two weeks, as described

above. Test compounds were administered orally in selected aqueous or oil based vehicles for up to 1 week. Serum was obtained and analyzed by precipitation or size exclusion chromatography for the relative abundance of VLDL, LDL and HDL. Results from testing in this model are summarized in

5 Table 13.

Alternatively, a strain of C57bl mouse was made to transgenically express human CETP. Plasma concentrations of hCETP ranged from 2-20  $\mu\text{g/ml}$ . The hCETP mice were made hypercholesterolemic by feeding cholesterol and fat supplemented chow for a minimum of two weeks, as  
10 described above. Test compounds were administered orally in selected aqueous or oil based vehicles for up to 1 week. Serum was obtained and analyzed by size exclusion chromatography for the relative abundance of VLDL, LDL and HDL. Results from testing in this model are summarized in Table 14.

15 Alternatively, cynomolgous monkeys were maintained on a normal chow diet. The compound corresponding to example 8 was dissolved in a corn oil based vehicle and administered by oral gavage at 10 mpk q.d. for up to 11 days. Plasma levels of drug were detected throughout the experiment in treated animals at ranges of 0.1-1.5  $\mu\text{g/mL}$ . Periodically, plasma samples  
20 were taken and analyzed for total cholesterol and HDL. After seven days, the treated animals exhibited a 2% increase in HDL and a 5% increase in total cholesterol, relative to vehicle-treated controls.

Alternatively, rabbits were maintained on a normal chow diet. The compound corresponding to example 8 was dissolved in a vehicle of  
25 ethanol:propylene glycol (1.5:18) and administered by Alzet pump at 30 mg/day/animal for up to 14 days. Plasma concentrations of drug were detected throughout the duration of the pump infusion in treated animals and averaged 1.2  $\mu\text{g/mL}$ . Periodically, plasma samples were taken and analyzed

for triglycerides, total cholesterol, and HDL. After fourteen days, the treated animals exhibited a 12% decrease in HDL, a 19% decrease in total cholesterol, as well as a 17% increase in triglycerides, compared to pre-dose levels.

11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65  
66  
67  
68  
69  
70  
71  
72  
73  
74  
75  
76  
77  
78  
79  
80  
81  
82  
83  
84  
85  
86  
87  
88  
89  
90  
91  
92  
93  
94  
95  
96  
97  
98  
99  
100  
101  
102  
103  
104  
105  
106  
107  
108  
109  
110  
111  
112  
113  
114  
115  
116  
117  
118  
119  
120  
121  
122  
123  
124  
125  
126  
127  
128  
129  
130  
131  
132  
133  
134  
135  
136  
137  
138  
139  
140  
141  
142  
143  
144  
145  
146  
147  
148  
149  
150  
151  
152  
153  
154  
155  
156  
157  
158  
159  
160  
161  
162  
163  
164  
165  
166  
167  
168  
169  
170  
171  
172  
173  
174  
175  
176  
177  
178  
179  
180  
181  
182  
183  
184  
185  
186  
187  
188  
189  
190  
191  
192  
193  
194  
195  
196  
197  
198  
199  
200  
201  
202  
203  
204  
205  
206  
207  
208  
209  
210  
211  
212  
213  
214  
215  
216  
217  
218  
219  
220  
221  
222  
223  
224  
225  
226  
227  
228  
229  
230  
231  
232  
233  
234  
235  
236  
237  
238  
239  
240  
241  
242  
243  
244  
245  
246  
247  
248  
249  
250  
251  
252  
253  
254  
255  
256  
257  
258  
259  
260  
261  
262  
263  
264  
265  
266  
267  
268  
269  
270  
271  
272  
273  
274  
275  
276  
277  
278  
279  
280  
281  
282  
283  
284  
285  
286  
287  
288  
289  
290  
291  
292  
293  
294  
295  
296  
297  
298  
299  
300  
301  
302  
303  
304  
305  
306  
307  
308  
309  
310  
311  
312  
313  
314  
315  
316  
317  
318  
319  
320  
321  
322  
323  
324  
325  
326  
327  
328  
329  
330  
331  
332  
333  
334  
335  
336  
337  
338  
339  
340  
341  
342  
343  
344  
345  
346  
347  
348  
349  
350  
351  
352  
353  
354  
355  
356  
357  
358  
359  
360  
361  
362  
363  
364  
365  
366  
367  
368  
369  
370  
371  
372  
373  
374  
375  
376  
377  
378  
379  
380  
381  
382  
383  
384  
385  
386  
387  
388  
389  
390  
391  
392  
393  
394  
395  
396  
397  
398  
399  
400  
401  
402  
403  
404  
405  
406  
407  
408  
409  
410  
411  
412  
413  
414  
415  
416  
417  
418  
419  
420  
421  
422  
423  
424  
425  
426  
427  
428  
429  
430  
431  
432  
433  
434  
435  
436  
437  
438  
439  
440  
441  
442  
443  
444  
445  
446  
447  
448  
449  
450  
451  
452  
453  
454  
455  
456  
457  
458  
459  
460  
461  
462  
463  
464  
465  
466  
467  
468  
469  
470  
471  
472  
473  
474  
475  
476  
477  
478  
479  
480  
481  
482  
483  
484  
485  
486  
487  
488  
489  
490  
491  
492  
493  
494  
495  
496  
497  
498  
499  
500  
501  
502  
503  
504  
505  
506  
507  
508  
509  
510  
511  
512  
513  
514  
515  
516  
517  
518  
519  
520  
521  
522  
523  
524  
525  
526  
527  
528  
529  
530  
531  
532  
533  
534  
535  
536  
537  
538  
539  
540  
541  
542  
543  
544  
545  
546  
547  
548  
549  
550  
551  
552  
553  
554  
555  
556  
557  
558  
559  
560  
561  
562  
563  
564  
565  
566  
567  
568  
569  
570  
571  
572  
573  
574  
575  
576  
577  
578  
579  
580  
581  
582  
583  
584  
585  
586  
587  
588  
589  
590  
591  
592  
593  
594  
595  
596  
597  
598  
599  
600  
601  
602  
603  
604  
605  
606  
607  
608  
609  
610  
611  
612  
613  
614  
615  
616  
617  
618  
619  
620  
621  
622  
623  
624  
625  
626  
627  
628  
629  
630  
631  
632  
633  
634  
635  
636  
637  
638  
639  
640  
641  
642  
643  
644  
645  
646  
647  
648  
649  
650  
651  
652  
653  
654  
655  
656  
657  
658  
659  
660  
661  
662  
663  
664  
665  
666  
667  
668  
669  
670  
671  
672  
673  
674  
675  
676  
677  
678  
679  
680  
681  
682  
683  
684  
685  
686  
687  
688  
689  
690  
691  
692  
693  
694  
695  
696  
697  
698  
699  
700  
701  
702  
703  
704  
705  
706  
707  
708  
709  
710  
711  
712  
713  
714  
715  
716  
717  
718  
719  
720  
721  
722  
723  
724  
725  
726  
727  
728  
729  
730  
731  
732  
733  
734  
735  
736  
737  
738  
739  
740  
741  
742  
743  
744  
745  
746  
747  
748  
749  
750  
751  
752  
753  
754  
755  
756  
757  
758  
759  
760  
761  
762  
763  
764  
765  
766  
767  
768  
769  
770  
771  
772  
773  
774  
775  
776  
777  
778  
779  
780  
781  
782  
783  
784  
785  
786  
787  
788  
789  
790  
791  
792  
793  
794  
795  
796  
797  
798  
799  
800  
801  
802  
803  
804  
805  
806  
807  
808  
809  
810  
811  
812  
813  
814  
815  
816  
817  
818  
819  
820  
821  
822  
823  
824  
825  
826  
827  
828  
829  
830  
831  
832  
833  
834  
835  
836  
837  
838  
839  
840  
841  
842  
843  
844  
845  
846  
847  
848  
849  
850  
851  
852  
853  
854  
855  
856  
857  
858  
859  
860  
861  
862  
863  
864  
865  
866  
867  
868  
869  
870  
871  
872  
873  
874  
875  
876  
877  
878  
879  
880  
881  
882  
883  
884  
885  
886  
887  
888  
889  
890  
891  
892  
893  
894  
895  
896  
897  
898  
899  
900  
901  
902  
903  
904  
905  
906  
907  
908  
909  
910  
911  
912  
913  
914  
915  
916  
917  
918  
919  
920  
921  
922  
923  
924  
925  
926  
927  
928  
929  
930  
931  
932  
933  
934  
935  
936  
937  
938  
939  
940  
941  
942  
943  
944  
945  
946  
947  
948  
949  
950  
951  
952  
953  
954  
955  
956  
957  
958  
959  
960  
961  
962  
963  
964  
965  
966  
967  
968  
969  
970  
971  
972  
973  
974  
975  
976  
977  
978  
979  
980  
981  
982  
983  
984  
985  
986  
987  
988  
989  
990  
991  
992  
993  
994  
995  
996  
997  
998  
999  
1000  
1001  
1002  
1003  
1004  
1005  
1006  
1007  
1008  
1009  
1010  
1011  
1012  
1013  
1014  
1015  
1016  
1017  
1018  
1019  
1020  
1021  
1022  
1023  
1024  
1025  
1026  
1027  
1028  
1029  
1030  
1031  
1032  
1033  
1034  
1035  
1036  
1037  
1038  
1039  
1040  
1041  
1042  
1043  
1044  
1045  
1046  
1047  
1048  
1049  
1050  
1051  
1052  
1053  
1054  
1055  
1056  
1057  
1058  
1059  
1060  
1061  
1062  
1063  
1064  
1065  
1066  
1067  
1068  
1069  
1070  
1071  
1072  
1073  
1074  
1075  
1076  
1077  
1078  
1079  
1080  
1081  
1082  
1083  
1084  
1085  
1086  
1087  
1088  
1089  
1090  
1091  
1092  
1093  
1094  
1095  
1096  
1097  
1098  
1099  
1100  
1101  
1102  
1103  
1104  
1105  
1106  
1107  
1108  
1109  
1110  
1111  
1112  
1113  
1114  
1115  
1116  
1117  
1118  
1119  
1120  
1121  
1122  
1123  
1124  
1125  
1126  
1127  
1128  
1129  
1130  
1131  
1132  
1133  
1134  
1135  
1136  
1137  
1138  
1139  
1140  
1141  
1142  
1143  
1144  
1145  
1146  
1147  
1148  
1149  
1150  
1151  
1152  
1153  
1154  
1155  
1156  
1157  
1158  
1159  
1160  
1161  
1162  
1163  
1164  
1165  
1166  
1167  
1168  
1169  
1170  
1171  
1172  
1173  
1174  
1175  
1176  
1177  
1178  
1179  
1180  
1181  
1182  
1183  
1184  
1185  
1186  
1187  
1188  
1189  
1190  
1191  
1192  
1193  
1194  
1195  
1196  
1197  
1198  
1199  
1200  
1201  
1202  
1203  
1204  
1205  
1206  
1207  
1208  
1209  
1210  
1211  
1212  
1213  
1214  
1215  
1216  
1217  
1218  
1219  
1220  
1221  
1222  
1223  
1224  
1225  
1226  
1227  
1228  
1229  
1230  
1231  
1232  
1233  
1234  
1235  
1236  
1237  
1238  
1239  
1240  
1241  
1242  
1243  
1244  
1245  
1246  
1247  
1248  
1249  
1250  
1251  
1252  
1253  
1254  
1255  
1256  
1257  
1258  
1259  
1260  
1261  
1262  
1263  
1264  
1265  
1266  
1267  
1268  
1269  
1270  
1271  
1272  
1273  
1274  
1275  
1276  
1277  
1278  
1279  
1280  
1281  
1282  
1283  
1284  
1285  
1286  
1287  
1288  
1289  
1290  
1291  
1292  
1293  
1294  
1295  
1296  
1297  
1298  
1299  
1300  
1301  
1302  
1303  
1304  
1305  
1306  
1307  
1308  
1309  
1310  
1311  
1312  
1313  
1314  
1315  
1316  
1317  
1318  
1319  
1320  
1321  
1322  
1323  
1324  
1325  
1326  
1327  
1328  
1329  
1330  
1331  
1332  
1333  
1334  
1335  
1336  
1337  
1338  
1339  
1340  
1341  
1342  
1343  
1344  
1345  
1346  
1347  
1348  
1349  
1350  
1351  
1352  
1353  
1354  
1355  
1356  
1357  
1358  
1359  
1360  
1361  
1362  
1363  
1364  
1365  
1366  
1367  
1368  
1369  
1370  
1371  
1372  
1373  
1374  
1375  
1376  
1377  
1378  
1379  
1380  
1381  
1382  
1383  
1384  
1385  
1386  
1387  
1388  
1389  
1390  
1391  
1392  
1393  
1394  
1395  
1396  
1397  
1398  
1399  
1400  
1401  
1402  
1403  
1404  
1405  
1406  
1407  
1408  
1409  
1410  
1411  
1412  
1413  
1414  
1415  
1416  
1417  
1418  
1419  
1420  
1421  
1422  
1423  
1424  
1425  
1426  
1427  
1428  
1429  
1430  
1431  
1432  
1433  
1434  
1435  
1436  
1437  
1438  
1439  
1440  
1441  
1442  
1443  
1444  
1445  
1446  
1447  
1448  
1449  
1450  
1451  
1452  
1453  
1454  
1455  
1456  
1457  
1458  
1459  
1460  
1461  
1462  
1463  
1464  
1465  
1466  
1467  
1468  
1469  
1470  
1471  
1472  
1473  
1474  
1475  
1476  
1477  
1478  
1479  
1480  
1481  
1482  
1483  
1484  
1485  
1486  
1487  
1488  
1489  
1490  
1491  
1492  
1493  
1494  
1495  
1496  
1497  
1498  
1499  
1500  
1501  
1502  
1503  
1504  
1505  
1506  
1507  
1508  
1509  
1510  
1511  
1512  
1513  
1514  
1515  
1516  
1517  
1518  
1519  
1520  
1521  
1522  
1523  
1524  
1525  
1526  
1527  
1528  
1529  
1530  
1531  
1532  
1533  
1534  
1535  
1536  
1537  
1538  
1539  
1540  
1541  
1542  
1543  
1544  
1545  
1546  
1547  
1548  
1549  
1550  
1551  
1552  
1553  
1554  
1555  
1556  
1557  
1558  
1559  
1560  
1561  
1562  
1563  
1564  
1565  
1566  
1567  
1568  
1569  
1570  
1571  
1572  
1573  
1574  
1575  
1576  
1577  
1578  
1579  
1580  
1581  
1582  
1583  
1584  
1585  
1586  
1587  
1588  
1589  
1590  
1591  
1592  
1593  
1594  
1595  
1596  
1597  
1598  
1599  
1600  
1601  
1602  
1603  
1604  
1605  
1606  
1607  
1608  
1609  
1610  
1611  
1612  
1613  
1614  
1615  
1616  
1617  
1618  
1619  
1620  
1621  
1622  
1623  
1624  
1625  
1626  
1627  
1628  
1629  
1630  
1631  
1632  
1633  
1634  
1635  
1636  
1637  
1638  
1639  
1640  
1641  
1642  
1643  
1644  
1645  
1646  
1647  
1648  
1649  
1650  
1651  
1652  
1653  
1654  
1655  
1656  
1657  
1658  
1659  
1660  
1661  
1662  
1663  
1664  
1665  
1666  
1667  
1668  
1669  
1670  
1671  
1672  
1673  
1674  
1675  
1676  
1677  
1678  
1679  
1680  
1681  
1682  
1683  
1684  
1685  
1686  
1687  
1688  
1689  
1690  
1691  
1692  
1693  
1694  
1695  
1696  
1697  
1698  
1699  
1700  
1701  
1702  
1703  
1704  
1705  
1706  
1707  
1708  
1709  
1710  
1711  
1712  
1713  
1714  
1715  
1716  
1717  
1718  
1719  
1720  
1721  
1722  
1723  
1724  
1725  
1726  
1727  
1728  
1729  
1730  
1731  
1732  
1733  
1734  
1735  
1736  
1737  
1738  
1739  
1740  
1741  
1742  
1743  
1744  
1745  
1746  
1747  
1748  
1749  
1750  
1751  
1752  
1753  
1754  
1755  
1756  
1757  
1758  
1759  
1760  
1761  
1762  
1763  
1764  
1765  
1766  
1767  
1768  
1769  
1770  
1771  
1772  
1773  
1774  
1775  
1776  
1777  
1778  
1779  
1780  
1781  
1782  
1783  
1784  
1785  
1786  
1787  
1788  
1789  
1790  
1791  
1792  
1793  
1794  
1795  
1796  
1797  
1798  
1799  
1800  
1801  
1802  
1803  
1804  
1805  
1806  
1807  
1808  
1809  
1810  
1811  
1812  
1813  
1814  
1815  
1816  
1817  
1818  
1819  
1820  
1821  
1822  
1823  
1824  
1825  
1826  
1827  
1828  
1829  
1830  
1831  
1832  
1833  
1834  
1835  
1836  
1837  
1838  
1839  
1840  
1841  
1842  
1843  
1844  
1845  
1846  
1847  
1848  
1849  
1850  
1851  
1852  
1853  
1854  
1855  
1856  
1857  
1858  
1859  
1860  
1861  
1862  
1863  
1864  
1865  
1866  
1867  
1868  
1869  
1870  
1871  
1872  
1873  
1874  
1875  
1876  
1877  
1878  
1879  
1880  
1881  
1882  
1883  
1884  
1885  
1886  
1887  
1888  
1889  
1890  
1891  
1892  
1893  
1894  
1895  
1896  
1897  
1898  
1899  
1900  
1901  
1902  
1903  
1904  
1905  
1906  
1907  
1908  
1909  
1910  
1911  
1912  
1913  
1914  
1915  
1916  
1917  
1918  
1919  
1920  
1921  
1922  
1923  
1924  
1925  
1926  
1927  
1928  
1929  
1930  
1931  
1932  
1933  
1934  
1935  
1936  
1937  
1938  
1939  
1940  
1941  
1942  
1943  
1944  
1945  
1946  
1947  
1948  
1949  
1950  
1951  
1952  
1953  
1954  
1955  
1956  
1957  
1958  
1959  
1960  
1961  
1962  
1963  
1964  
1965  
1966  
1967  
1968  
1969  
1970  
1971  
1972  
1973  
1974  
1975  
1976  
1977  
1978  
1979  
1980  
1981  
1982  
1983  
1984  
1985  
1986  
1987  
1988  
1989  
1990  
1991  
1992  
1993  
1994  
1995  
1996  
1997  
1998  
1999  
2000  
2001  
2002  
2003  
2004  
2005  
2006  
2007  
2008  
2009  
2010  
2011  
2012  
2013  
2014  
2015  
2016  
2017  
2018  
2019  
2020  
2021  
2022  
2023  
2024  
2025  
2026  
2027  
2028  
2029  
2030  
2031  
2032  
2033  
2034  
2035  
2036  
2037  
2038  
2039  
2040  
2041  
2042  
2043  
2044  
2045  
2046  
2047  
2048  
2049  
2050  
2051  
2052  
2053  
2054  
2055  
2056  
2057  
2058  
2059  
2060  
2061  
2062  
2063  
2064  
2065  
2066  
2067  
2068  
2069  
2070  
2071  
2072  
2073  
2074  
2075  
2076  
2077  
2078  
2079  
2080  
2081  
2082  
2083  
2084  
2085  
2086  
2087  
2088  
2089  
2090  
2091  
2092  
2093  
2094  
2095  
2096  
2097  
2098  
2099  
2100  
2101  
2102  
2103  
2104  
2105  
2106  
2107  
2108  
2109  
2110  
2111  
2112  
2113  
2114  
2115  
2116  
2117  
2118  
2119  
2120  
2121  
2122  
2123  
2124  
2125  
2126  
2127  
2128  
2129  
2130  
2131  
2132  
2133  
2134  
2135  
2136  
2137  
2138  
2139  
2140  
2141  
2142  
2143  
2144  
2145  
2146  
2147  
2148  
2149  
2150  
2151  
2152  
2153  
2154  
2155  
2156  
2157  
2158  
2159  
2160  
2161  
2162  
2163  
2164  
2165  
2166  
2167  
2168  
2169  
2170  
2171  
2172  
2173  
2174  
2175  
2176  
2177  
2178  
2179  
2180  
2181  
2182  
2183  
2184  
2185  
2186  
2187  
2188  
2189  
2190  
2191  
2192  
2193  
2194  
2195  
2196  
2197  
2198  
2199  
2200  
2201  
2202  
2203  
2204  
2205  
2206  
2207  
2208  
2209  
2210  
2211  
2212  
2213  
2214  
2215  
2216  
2217  
2218  
2219  
2220  
2221  
2222  
2223  
2224  
2225  
2226  
2227  
2228  
2

Table 9. Inhibition of CETP Activity by Examples in Reconstituted Buffer Assay.

<u>Ex.</u> <u>No.</u>	<u>IC<sub>50</sub></u> <u>(<math>\mu</math>M)</u>	<u>Ex.</u> <u>No.</u>	<u>IC<sub>50</sub></u> <u>(<math>\mu</math>M)</u>
8	0.0008	42	0.38
11	0.001	27	0.44
19	0.004	26	0.53
9	0.008	29	0.72
10	0.012	3	0.76
2	0.014	28	0.86
4	0.014	32	1.2
20	0.027	25	1.4
22	0.027	39	1.6
12	0.034	15	1.6
14	0.04	30	2.7
18	0.044	33B	3.2
16	0.049	5	3.4
43	0.058	31	3.5
23	0.066	7	4.9
34	0.076	44	6.8
41	0.086	17	18
21	0.11	6	68
13	0.13	44A	> 50
1	0.14		
33	0.15		
38	0.18		
36	0.20		
37	0.21		
40	0.23		
35	0.28		
24	0.33		

Table 10. Inhibition of CETP Activity by  
Examples in Human Plasma Assay.

<u>Ex.</u> <u>No.</u>	<u>IC<sub>50</sub></u> ( $\mu$ M)
8	0.049
11	0.072
10	0.11
22	0.14
19	0.19
20	0.3
18	0.44
14	0.59
9	0.62
2	0.65
4	0.65
16	0.77
12	0.79
34	1.4
43	1.5
23	2.0
1	5.6
41	7.2
42	11
3	20

Table 11. Inhibition of CETP-mediated Transfer in Hamster

<b>Ex. No.</b>	<b>Single Oral Dose</b>	<b>% Inhibition of Transfer</b>
8	10 mpk	35

Table 12. Inhibition of CETP-mediated Transfer in hCETP Mice.

Ex. No.	Single Oral Dose	% Inhibition of Transfer
8	60 mpk	40

Table 13. Change in Lipoprotein Profile in Hamster.

Ex. No.	Oral Dose qd, 5 days	% Change in Lipoprotein Profile		
		HDL	LDL	VLDL
8	30 mpk	12	-12	-22

Table 14. Change in Lipoprotein Profile in hCETP Mice.

Ex. No.	Oral Dose qd, 5 days	% Change in Lipoprotein Profile		
		HDL	LDL	VLDL
8	30 mpk	12	20	--